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(54) Title: SOLUBLE HETERODIMERIC CYTOKINE RECEPTOR

(57) Abstract: A soluble receptor that binds to IL-20 having two polypeptide subunits, IL-22R and IL-20RB. The two subunits are preferably linked together. In one embodiment one subunit is fused to the constant region of the light chain of an immunoglobulin, and the other subunit is fused to the constant region of the heavy chain of the immunoglobulin. The light chain and the heavy chain are connected via a disulfide bond.

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SOLUBLE HETERODIMERIC CYTOKINE RECEPTOR

BACKGROUND OF THE INVENTION

The teachings of all of the references cited herein are incorporated in their entirety herein by reference.

10 Cytokines are soluble proteins that influence the growth and differentiation of many cell types. Their receptors are composed of one or more integral membrane proteins that bind the cytokine with high affinity and transduce this binding event to the cell through the cytoplasmic portions of the certain receptor subunits. Cytokine receptors have been grouped into several classes on the basis of similarities in
15 their extracellular ligand binding domains. For example, the receptor chains responsible for binding and/or transducing the effect of interferons (IFNs) are members of the type II cytokine receptor family (CRF2), based upon a characteristic 200 residue extracellular domain. The demonstrated *in vivo* activities of these interferons illustrate the enormous clinical potential of, and need for, other cytokines, cytokine agonists, and
20 cytokine antagonists. Some cytokines are involved in the inflammatory cascade and can promote such diseases as rheumatoid arthritis, Crohn's disease, psoriasis, heart disease etc. Thus, there is a need to discover cytokines and their receptors that are involved in inflammation. One can then use the isolated soluble receptors of the cytokine to inhibit the cytokine-mediated inflammation.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES 1-8 are schematic representations of different embodiments of the soluble receptor of the present invention

30 DESCRIPTION OF THE INVENTION

The present invention fills this need by providing a newly discovered soluble receptor that binds to Interleukin-20 (IL-20). The soluble receptor can be used to down-regulate IL-20 and thus treat inflammatory diseases such as psoriasis and inflammatory lung diseases.

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IL-20 was formally called 'Zcyto10', (International Patent Publication No. WO 99/27103) and has the amino acid sequences of SEQ ID NOs: 1-9. A heterodimeric receptor that binds to IL-20 is comprised of two chains, an alpha chain

and a beta chain. The alpha chain is referred to as IL-22R (formerly called Zcytor11). See U.S. Patent No. 5,965,704. The beta chain, hereinafter referred to as IL-20RB, was formally called DIRS1. See International Patent Application No. PCT/US99/03735. The present invention is a soluble receptor comprised of the extracellular domain of IL-
5 22R and the extracellular domain of IL-20RB.

The present invention encompasses an isolated soluble receptor comprised of a 'IL-22R' subunit and an 'IL-20RB' subunit, wherein the IL-22R subunit is comprised of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 12 and 13, and the IL-20RB subunit is comprised of a
10 polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14-23. The IL-22R and IL-20RB subunits are generally linked together by a polypeptide linker. The linking can be by any means but generally by a peptide bond or a disulfide bond between a polypeptide connected to the IL-22R subunit and a polypeptide connected to the IL-20RB subunit. The present invention is also directed
15 towards isolated polynucleotides that encode the novel IL-22R and IL-20RB polypeptides of the present invention.

In one embodiment the IL-22R subunit is fused to the constant region of the heavy chain of an immunoglobulin (Ig) molecule or a portion thereof and the IL-20RB subunit is fused to the constant region of the light chain of an Ig molecule such
20 that the constant region of the light chain is disulfide bonded to the constant region of the heavy chain, generally to a cysteine residue on the hinge region of the heavy chain. Also the opposite can occur, the IL-22R subunit can be fused to the constant region of the light chain of an Ig molecule and the IL-20RB subunit can be fused to the constant region of the heavy chain of an Ig molecule.

25 In one embodiment of the soluble receptor of the present invention, the IL-22R subunit fused to the constant region of the heavy chain is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 25, 26, 31 and 32 and the IL-20RB subunit fused to the constant region of the light chain of the Ig molecule is comprised of an amino acid sequence selected from the group consisting of
30 SEQ ID NOs: 28 and 29.

The present invention is further directed to a method for inhibiting interleukin-20 (IL-20) comprising administering to an individual a soluble IL-22R/IL-20RB heterodimeric polypeptide.

The present invention is also directed to a method for inhibiting IL-20
5 comprising administering to an antibody that binds to IL-22R.

The present invention is further directed to a polynucleotide encoding for the extracellular domain of IL-22R and the extracellular domain of IL-20RB. An example of such a polynucleotide is a vector or plasmid containing a polynucleotide that encodes for IL-22R and IL-20RB.

10

Definitions

Prior to setting forth the invention in more detail, it may be helpful to the understanding thereof to define the following terms.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to
15 denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete
20 polypeptide.

As used herein, the term "antibody fusion protein" refers to a recombinant molecule that comprises an antibody component and a therapeutic agent. Examples of therapeutic agents suitable for such fusion proteins include immunomodulators ("antibody-immunomodulator fusion protein") and toxins
25 ("antibody-toxin fusion protein").

The term "complement/anti-complement pair" denotes non-identical moieties that form a non-covalently associated, stable pair under appropriate conditions. For instance, biotin and avidin (or streptavidin) are prototypical members of a complement/anti-complement pair. Other exemplary complement/anti-complement
30 pairs include receptor/ligand pairs, antibody/antigen (or hapten or epitope) pairs, sense/antisense polynucleotide pairs, and the like. Where subsequent dissociation of the complement/anti-complement pair is desirable, the complement/anti-complement pair preferably has a binding affinity of $<10^9 \text{ M}^{-1}$.

The term "complements of a polynucleotide molecule" is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence.

The term "contig" denotes a polynucleotide that has a contiguous stretch
5 of identical or complementary sequence to another polynucleotide. Contiguous sequences are said to "overlap" a given stretch of polynucleotide sequence either in their entirety or along a partial stretch of the polynucleotide.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference
10 polynucleotide molecule that encodes a polypeptide). Degenerate codons contain different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked
15 to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

20 The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic
25 clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78 (1985)).

30 An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide is substantially free of other polypeptides, particularly other polypeptides of animal origin. It is preferred to provide the polypeptides in a highly purified form, i.e. greater than 95% pure, more preferably
35 greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

The term "operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, *e.g.*, transcription initiates in the promoter and proceeds through the coding segment to the terminator.

5 A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides
10 ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length
15 and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nucleotides in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10
20 amino acid residues are commonly referred to as "peptides".

The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

25 A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures;
30 substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

The term "receptor" denotes a cell-associated protein that binds to a bioactive molecule (i.e., a ligand) and mediates the effect of the ligand on the cell. Membrane-bound receptors are characterized by a multi-domain structure comprising
35 an extracellular ligand-binding domain and an intracellular effector domain that is typically involved in signal transduction. Binding of ligand to receptor results in a conformational change in the receptor that causes an interaction between the effector

domain and other molecule(s) in the cell. This interaction in turn leads to an alteration in the metabolism of the cell. Metabolic events that are linked to receptor-ligand interactions include gene transcription, phosphorylation, dephosphorylation, increases in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. In general, receptors can be membrane bound, cytosolic or nuclear, monomeric (*e.g.*, thyroid stimulating hormone receptor, beta-adrenergic receptor) or multimeric (*e.g.*, PDGF receptor, growth hormone receptor, IL-3 receptor, GM-CSF receptor, G-CSF receptor, erythropoietin receptor and IL-6 receptor).

10 The term "secretory signal sequence" denotes a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

15 The term "splice variant" is used herein to denote alternative forms of RNA transcribed from a gene. Splice variation arises naturally through use of alternative splicing sites within a transcribed RNA molecule, or less commonly between separately transcribed RNA molecules, and may result in several mRNAs transcribed from the same gene. Splice variants may encode polypeptides having altered amino acid sequence. The term splice variant is also used herein to denote a protein encoded by a splice variant of an mRNA transcribed from a gene.

20 Molecular weights and lengths of polymers determined by imprecise analytical methods (*e.g.*, gel electrophoresis) will be understood to be approximate values. When such a value is expressed as "about" X or "approximately" X, the stated value of X will be understood to be accurate to $\pm 10\%$.

25 As was stated above, IL-20 (formally called Zcyto10) is defined and methods for producing it and antibodies to IL-20 are contained in International Patent Application No. PCT/US98/25228, publication no. WO 99/27103, published November 25, 1998 and U.S. Patent Application No. 09/313,458 filed May 17, 1999. The polynucleotide and polypeptide of human IL-20 are represented by SEQ ID NOs: 1 - 4, and mouse IL-20 by SEQ ID NOs: 5-9.

30 A receptor that binds to IL-20 has been discovered and is a heterodimer comprised of the polypeptide termed 'IL-22R' and a polypeptide termed 'IL-20RB'. The IL-22R, also called ZcytoR11, polypeptide, nucleic acid that encodes it, antibodies to IL-22R, and methods for producing it are disclosed in U.S. Patent No. 5,965,704 issued October 12, 1999. SEQ ID NOs: 10 - 12 are the IL-22R polynucleotides and

polypeptides. The extracellular domain of the human IL-22R is comprised of either SEQ ID NO: 12 or SEQ ID NO: 13.

The extracellular domain of IL-20RB (SEQ ID NOs: 14-15, and a variant SEQ ID NOs: 22 and 23) is comprised of a polypeptide selected from the group consisting of SEQ ID NOs: 16-21. Preferably, the extracellular domain of the IL-22R polypeptide and the extracellular domain of the IL-20RB polypeptide are covalently linked together. In a preferred embodiment one extracellular subunit polypeptide has a constant region of a heavy chain of an immunoglobulin fused to its carboxy terminus and the other extracellular subunit has a constant light chain of an immunoglobulin (Ig) fused to its carboxy terminus such that the two polypeptides come together to form a soluble receptor and a disulfide bond is formed between the heavy and the light Ig chains. In another embodiment, a peptide linker could be fused to the two carboxy-termini of the polypeptides to form a covalently bonded soluble receptor.

SEQ ID NOs: 24 and 25 are constructs of the extracellular domain of IL-22R fused to a mutated human immunoglobulin gamma 1 constant region. SEQ ID NO: 26 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 27 and 28 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region. SEQ ID NO: 29 is the predicted mature sequence without the signal sequence. Figure 1 is a schematic representation of the heterotetramer.

SEQ ID NOs: 30 and 31 are constructs of the extracellular domain of IL-22R fused to a mutated human immunoglobulin gamma 1 constant region. SEQ ID NO: 32 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 33 and 34 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region produced according to the procedure of example 12. SEQ ID NO: 35 is the predicted mature sequence without the signal sequence. The resultant heterotetramer does not have a polypeptide linker between the extracellular domains and the beginning of the Ig constant regions, 22 in Figure 1. Hereinafter, the term "extracellular domain of a receptor" means the extracellular domain of the receptor or a portion of the extracellular domain that is necessary for binding to its ligand, in this case the ligand being IL-20.

One can link together the extracellular domains of IL-22R and IL-20RB in a number of ways such that the resultant soluble receptor can bind to IL-20. Figures 1-8 illustrate a representative number of embodiments of the present invention. Common elements in each of the drawings are given the same number. Figure 1 represents the embodiment of the present invention of SEQ ID NOs: 24, 25, 26, 27, 28 and 29. The soluble receptor construct, designated 10, is comprised of two IL-20

binding site polypeptide chains designated 12 and 14. Each binding site is comprised of the extracellular domain of IL-22R, designated 16, and the extracellular domain of IL-20RB designated 18.

5 The extracellular domain, 16, of IL-22R is linked to the constant heavy one (CH1) domain, 20, of the human immunoglobulin gamma 1 heavy chain constant region via linker 22, which is SEQ ID NO: 36. The CH1 domain, 20, is then linked to the CH2 domain, 24, via hinge region 23. The CH2 domain, 24, is linked to the CH3 domain, 26, via hinge region 25.

10 Comparing the construct of Figure 1 with SEQ ID NO:25, the mature extracellular domain, 16, of IL-22R extends from amino acid residues 18, a proline, to and including amino acid residue 228, a threonine of SEQ ID NO:25. Polypeptide linker, 22, extends from amino acid residue 229, a glycine to and including amino acid residue 243, a serine, of SEQ ID NO:25. The CH1 domain, 22 of Figure 1, extends from amino acid residue 244, an alanine, to and including amino acid residue 341, a
15 valine, of SEQ ID NO: 25. Hinge region 23 of Figure 1 extends from amino acid residue 342, a glutamic acid to and including amino acid residue 356, a proline, of SEQ ID NO: 25. Chains 12 and 14 are disulfide-bonded together by means of disulfide bonds 28 and 30. The disulfide bonds are formed between the heavy chains by the cysteine residues at positions 352 and 356 of SEQ ID NO: 25 of each of the two heavy chains.

20 Extracellular domain, 18, of IL-20RB is linked to the constant region of the human kappa light chain (CL), 34 of Figure 1 via polypeptide linker 32, which is the polypeptide SEQ ID NO: 36. The extracellular domain, 18, of IL-20RB extends from amino acid residue 30, a valine, to and including amino acid residue 230, an alanine, of SEQ ID NO: 28. Polypeptide linker, 32, extends from amino acid residue 231, a
25 glycine, to and including amino acid residue 245, a serine, of SEQ ID NO: 28. The kappa constant light region, 34, extends from amino acid residue 246, an arginine, to and including the final amino acid residue 352, a cysteine, of SEQ ID NO: 28. The cysteine at position 352 of SEQ ID NO: 28 forms a disulfide bond, 36 in Figure 1, with the cysteine at position 346 of SEQ ID NO: 25. The constant light chain 34 is thus
30 linked to the hinge region, 23, by disulfide bond, 36. In this way, the extracellular domain, 16, of IL-22R is linked to the extracellular domain, 18, of IL-20RB to form a soluble receptor.

If the cysteine residues at positions 352 and 356 of SEQ ID NO: 25 were changed to different amino acid residues, the two IL-20 binding polypeptides, 12 and
35 14, would not be disulfide bonded together and would form a construct shown in Figure 2 having hinge region, 27.

Figure 3 shows a very simple soluble receptor 38 of the present invention wherein extracellular domain, 16, of IL-22R is connected to the extracellular domain, 18, of IL-20RB by means of a polypeptide linker, 40. The polypeptide linker extends from the amino terminus of extracellular domain, 16, of IL-22R and is
5 connected to the carboxyl terminus of the extracellular domain, 18, of IL-20RB. The polypeptide linker should be between 100-240 amino acids in length, preferably about 170 amino acid residues in length. A suitable linker would be comprised of glycine and serine residues. A possible linker would be multiple units of SEQ ID NO: 36, preferably about 12.

10 Figure 4 shows an embodiment that has the extracellular domain, 16, of IL-22R linked to the extracellular domain, 18, of IL-20RB by means of linker 40, as in Figure 3. While the extracellular domain, 16, of IL-22R is linked to the CH1 domain, 20, as in Figure 1 by means of polypeptide linker 42, which should be about 30 amino acid residues in length. An ideal linker would be comprised of glycine and serine as in
15 SEQ ID NO: 72, and the hinge sequence, 23 of Figure 1.

Figure 5 shows another possible embodiment of the present invention. In this embodiment, a polypeptide linker 44 of about 15 amino acid residue, *e.g.* SEQ ID NO: 36, links the carboxyl terminus of the extracellular domain, 18, of IL-20RB with the amino terminus of the extracellular domain, 16, of IL-22R. A polypeptide linker 46
20 of about 30 amino acid residues extends from the carboxy terminus of the extracellular domain, 16, of IL-22R to the CH2 domain. The carboxyl terminus of linker 46 would preferably be comprised of the hinge region extending from amino acid residue 342, a glutamic acid to and including amino acid residue 356, a proline, of SEQ ID NO: 25. Nonetheless, polypeptide linker 46 would ideally have at least one cysteine residue at
25 its carboxyl terminus so a disulfide bond could be formed.

The soluble IL-20 receptor of Figure 6 is identical to that of Figure 1 except for the CH3 domain, 26 of Figure 1, is not present on the embodiment of Figure 6. The CH3 region begins at amino acid residue 467, a glycine, and extends to the last residue 573 of SEQ ID NO: 25.

30 Figure 7 shows a soluble IL-20 receptor construct that is identical to the construct of Figure 1 except both the CH2, and CH3 domains are absent. The CH2 and CH3 domains run from amino acid residue 357, an alanine, to the end of the polypeptide sequence of SEQ ID NO: 25.

Figure 8 shows a construct wherein both IL-22R, 16, and IL-20RB have
35 a polypeptide linker, 48, fused to their respective carboxyl termini. Each polypeptide linker has two cysteine residues such that when they are expressed the cysteines form two disulfide bonds, 50 and 52. In this case the polypeptide linker is comprised of the

hinge region, 23 in Figure 1. The hinge region is comprised of amino acid residues 342, a glutamic acid, to and including amino acid residue 356 of SEQ ID NO: 25.

- In another aspect of the invention, a method is provided for producing a soluble receptor comprised of extracellular domains of IL-22R and IL-20RB
- 5 comprising (a) introducing into a host cell a first DNA sequence comprised of a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-22R and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a
- 10 transcriptional promoter operatively linked to a second secretory signal followed downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-20RB and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under
- 15 physiological conditions to allow the secretion of a fusion protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA
- 20 sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region.

- In an alternative embodiment, a method is provided for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of a
- 25 transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-20RB and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a transcriptional promoter operatively linked to a second secretory signal followed
- 30 downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-22R and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the production of a dimerized heterodimeric fusion
- 35 protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the dimerized polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the

hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region. (See U.S. Patent No. 5,843,725.)

5 In another embodiment, a method is provided for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a DNA construct containing a DNA construct that encodes the extracellular portion of IL-20RB and a DNA construct of the extracellular portion of IL-22R, (b) growing the host cell in an appropriate medium under physiological
10 conditions to allow the production of the extracellular domain of IL-22R and the extracellular domain of IL-20RB; and (d) isolating the polypeptides from the host cell.

Other aspects of the present invention include host cells transformed or transfected with a DNA construct that encodes the extracellular domain of IL-22RB and a DNA construct that encodes the extracellular domain of IL-20RB. Both constructs can
15 be on one vector or on separate vectors.

A polynucleotide, generally a cDNA sequence, encodes the described polypeptides herein. A cDNA sequence that encodes a polypeptide of the present invention is comprised of a series of codons, each amino acid residue of the polypeptide being encoded by a codon and each codon being comprised of three nucleotides. The
20 amino acid residues are encoded by their respective codons as follows.

Alanine (Ala) is encoded by GCA, GCC, GCG or GCT.
Cysteine (Cys) is encoded by TGC or TGT.
25 Aspartic acid (Asp) is encoded by GAC or GAT.
Glutamic acid (Glu) is encoded by GAA or GAG.
Phenylalanine (Phe) is encoded by TTC or TTT.
Glycine (Gly) is encoded by GGA, GGC, GGG or GGT.
Histidine (His) is encoded by CAC or CAT.
30 Isoleucine (Ile) is encoded by ATA, ATC or ATT.
Lysine (Lys) is encoded by AAA, or AAG.
Leucine (Leu) is encoded by TTA, TTG, CTA, CTC, CTG or CTT.
Methionine (Met) is encoded by ATG.
Asparagine (Asn) is encoded by AAC or AAT.
35 Proline (Pro) is encoded by CCA, CCC, CCG or CCT.
Glutamine (Gln) is encoded by CAA or CAG.
Arginine (Arg) is encoded by AGA, AGG, CGA, CGC, CGG or CGT.

Serine (Ser) is encoded by AGC, AGT, TCA, TCC, TCG or TCT.

Threonine (Thr) is encoded by ACA, ACC, ACG or ACT.

Valine (Val) is encoded by GTA, GTC, GTG or GTT.

Tryptophan (Trp) is encoded by TGG.

5 Tyrosine (Tyr) is encoded by TAC or TAT.

It is to be recognized that according to the present invention, when a polynucleotide is claimed as described herein, it is understood that what is claimed are both the sense strand, the anti-sense strand, and the DNA as double-stranded having
10 both the sense and anti-sense strand annealed together by their respective hydrogen bonds. Also claimed is the messenger RNA (mRNA) that encodes the polypeptides of the present invention, and which mRNA is encoded by the cDNA described herein. Messenger RNA (mRNA) will encode a polypeptide using the same codons as those defined herein, with the exception that each thymine nucleotide (T) is replaced by a
15 uracil nucleotide (U).

One of ordinary skill in the art will also appreciate that different species can exhibit "preferential codon usage." In general, see, Grantham, *et al.*, *Nuc. Acids Res.* 8:1893-1912 (1980); Haas, *et al. Curr. Biol.* 6:315-324 (1996); Wain-Hobson, *et al.*, *Gene* 13:355-364 (1981); Grosjean and Fiers, *Gene* 18:199-209 (1982); Holm, *Nuc.*
20 *Acids Res.* 14:3075-3087 (1986); Ikemura, *J. Mol. Biol.* 158:573-597 (1982). As used herein, the term "preferential codon usage" or "preferential codons" is a term of art referring to protein translation codons that are most frequently used in cells of a certain species, thus favoring one or a few representatives of the possible codons encoding each amino acid. For example, the amino acid Threonine (Thr) may be encoded by
25 ACA, ACC, ACG, or ACT, but in mammalian cells ACC is the most commonly used codon; in other species, for example, insect cells, yeast, viruses or bacteria, different Thr codons may be preferential. Preferential codons for a particular species can be introduced into the polynucleotides of the present invention by a variety of methods known in the art. Introduction of preferential codon sequences into recombinant DNA
30 can, for example, enhance production of the protein by making protein translation more efficient within a particular cell type or species. Sequences containing preferential codons can be tested and optimized for expression in various species, and tested for functionality as disclosed herein.

Methods for synthesizing amino acids and aminoacylating tRNA are
35 known in the art. Transcription and translation of plasmids containing nonsense mutations is carried out in a cell-free system comprising an *E. coli* S30 extract and

commercially available enzymes and other reagents. Proteins are purified by chromatography. See, for example, Robertson *et al.*, *J. Am. Chem. Soc.* 113:2722 (1991); Ellman *et al.*, *Methods Enzymol.* 202:301 (1991); Chung *et al.*, *Science* 259:806-809 (1993); and Chung *et al.*, *Proc. Natl. Acad. Sci. USA* 90:10145-1019 (1993). In a
5 second method, translation is carried out in *Xenopus* oocytes by microinjection of mutated mRNA and chemically aminoacylated suppressor tRNAs, Turcatti *et al.*, *J. Biol. Chem.* 271:19991-19998 (1996). Within a third method, *E. coli* cells are cultured in the absence of a natural amino acid that is to be replaced (*e.g.*, phenylalanine) and in the presence of the desired non-naturally occurring amino acid(s) (*e.g.*, 2-
10 azaphenylalanine, 3-azaphenylalanine, 4-azaphenylalanine, or 4-fluorophenylalanine). The non-naturally occurring amino acid is incorporated into the protein in place of its natural counterpart. See, Koide *et al.*, *Biochem.* 33:7470-7476 (1994). Naturally occurring amino acid residues can be converted to non-naturally occurring species by *in vitro* chemical modification. Chemical modification can be combined with site-
15 directed mutagenesis to further expand the range of substitutions, Wynn and Richards, *Protein Sci.* 2:395-403 (1993).

A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, non-naturally occurring amino acids, and unnatural amino acids may be substituted for amino acid residues.

20 Essential amino acids in the polypeptides of the present invention can be identified according to procedures known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis, Cunningham and Wells, *Science* 244: 1081-1085 (1989); Bass *et al.*, *Proc. Natl. Acad. Sci. USA* 88:4498-502 (1991). In the latter technique, single alanine mutations are introduced at every residue in the molecule, and
25 the resultant mutant molecules are tested for biological activity as disclosed below to identify amino acid residues that are critical to the activity of the molecule. See also, Hilton *et al.*, *J. Biol. Chem.* 271:4699-708, 1996. Sites of ligand-receptor interaction can also be determined by physical analysis of structure, as determined by such techniques as nuclear magnetic resonance, crystallography, electron diffraction or
30 photoaffinity labeling, in conjunction with mutation of putative contact site amino acids. See, for example, de Vos *et al.*, *Science* 255:306-312 (1992); Smith *et al.*, *J. Mol. Biol.* 224:899-904 (1992); Wlodaver *et al.*, *FEBS Lett.* 309:59-64 (1992).

Multiple amino acid substitutions can be made and tested using known methods of mutagenesis and screening, such as those disclosed by Reidhaar-Olson and
35 Sauer, *Science* 241:53-57 (1988) or Bowie and Sauer, *Proc. Natl. Acad. Sci. USA* 86:2152-2156 (1989). Briefly, these authors disclose methods for simultaneously randomizing two or more positions in a polypeptide, selecting for functional

polypeptide, and then sequencing the mutagenized polypeptides to determine the spectrum of allowable substitutions at each position. Other methods that can be used include phage display, *e.g.*, Lowman *et al.*, *Biochem.* 30:10832-10837 (1991); Ladner *et al.*, U.S. Patent No. 5,223,409; Huse, WIPO Publication WO 92/06204) and region-directed mutagenesis, Derbyshire *et al.*, *Gene* 46:145 (1986); Ner *et al.*, *DNA* 7:127 (1988).

Variants of the disclosed IL-20, IL-22R and IL-20RB DNA and polypeptide sequences can be generated through DNA shuffling as disclosed by Stemmer, *Nature* 370:389-391, (1994), Stemmer, *Proc. Natl. Acad. Sci. USA* 91:10747-10751 (1994) and WIPO Publication WO 97/20078. Briefly, variant DNAs are generated by *in vitro* homologous recombination by random fragmentation of a parent DNA followed by reassembly using PCR, resulting in randomly introduced point mutations. This technique can be modified by using a family of parent DNAs, such as allelic variants or DNAs from different species, to introduce additional variability into the process. Selection or screening for the desired activity, followed by additional iterations of mutagenesis and assay provides for rapid "evolution" of sequences by selecting for desirable mutations while simultaneously selecting against detrimental changes.

Mutagenesis methods as disclosed herein can be combined with high-throughput, automated screening methods to detect activity of cloned, mutagenized polypeptides in host cells. Mutagenized DNA molecules that encode active polypeptides can be recovered from the host cells and rapidly sequenced using modern equipment. These methods allow the rapid determination of the importance of individual amino acid residues in a polypeptide of interest, and can be applied to polypeptides of unknown structure.

PROTEIN PRODUCTION

Polypeptides can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are preferred. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd ed., (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and Ausubel *et al.*, eds., *Current Protocols in Molecular Biology* (John Wiley and Sons, Inc., NY, 1987).

In general, a DNA sequence encoding a polypeptide is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although
5 those skilled in the art will recognize that within certain systems selectable markers may be provided on separate vectors, and replication of the exogenous DNA may be provided by integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and
10 are available through commercial suppliers.

To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the native polypeptides, or may be derived from another secreted protein (*e.g.*, t-
15 PA) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized polypeptide into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the polypeptide of interest, although certain secretory signal sequences may be
20 positioned elsewhere in the DNA sequence of interest (see, *e.g.*, Welch *et al.*, U.S. Patent No. 5,037,743; Holland *et al.*, U.S. Patent No. 5,143,830).

Alternatively, the secretory signal sequence contained in the polypeptides of the present invention is used to direct other polypeptides into the secretory pathway. The present invention provides for such fusion polypeptides. The
25 secretory signal sequence contained in the fusion polypeptides of the present invention is preferably fused amino-terminally to an additional peptide to direct the additional peptide into the secretory pathway. Such constructs have numerous applications known in the art. For example, these novel secretory signal sequence fusion constructs can direct the secretion of an active component of a normally non-secreted protein, such as
30 a receptor. Such fusions may be used *in vivo* or *in vitro* to direct peptides through the secretory pathway.

Cultured mammalian cells are suitable hosts within the present invention. Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection, Wigler *et al.*, *Cell* 14:725 (1978), Corsaro
35 and Pearson, *Somatic Cell Genetics* 7:603 (1981); Graham and Van der Eb, *Virology* 52:456 (1973), electroporation, Neumann *et al.*, *EMBO J.* 1:841-845 (1982), DEAE-dextran mediated transfection (Ausubel *et al.*, *ibid.*, and liposome-mediated

transfection, Hawley-Nelson *et al.*, *Focus* 15:73 (1993); Ciccarone *et al.*, *Focus* 15:80 (1993), and viral vectors, Miller and Rosman, *BioTechniques* 7:980(1989); Wang and Finer, *Nature Med.* 2:714 (1996). The production of recombinant polypeptides in cultured mammalian cells is disclosed, for example, by Levinson *et al.*, U.S. Patent No. 5 4,713,339; Hagen *et al.*, U.S. Patent No. 4,784,950; Palmiter *et al.*, U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham *et al.*, *J. Gen. Virol.* 36:59 (1977) and Chinese hamster ovary (*e.g.* CHO- 10 K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, *e.g.*, U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 15 4,579,821 and 4,601,978) and the adenovirus major late promoter.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and are able to pass the gene of interest to their progeny are referred to as "stable 20 transfectants." A preferred selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective 25 agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. A preferred amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (*e.g.* hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used. Alternative markers that introduce an altered 30 phenotype, such as green fluorescent protein, or cell surface proteins such as CD4, CD8, Class I MHC, placental alkaline phosphatase may be used to sort transfected cells from untransfected cells by such means as FACS sorting or magnetic bead separation technology.

Other higher eukaryotic cells can also be used as hosts, including plant 35 cells, insect cells and avian cells. The use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar *et al.*, *J. Biosci. (Bangalore)* 11:47 (1987). Transformation of insect cells and production of foreign

polypeptides therein is disclosed by Guarino *et al.*, U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463. Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). DNA encoding a polypeptide is inserted into the baculoviral genome in place of the AcNPV polyhedrin gene coding sequence by one of two methods. The first is the traditional method of homologous DNA recombination between wild-type AcNPV and a transfer vector containing the gene flanked by AcNPV sequences. Suitable insect cells, *e.g.* SF9 cells, are infected with wild-type AcNPV and transfected with a transfer vector comprising a polynucleotide operably linked to an AcNPV polyhedrin gene promoter, terminator, and flanking sequences. See, King, L.A. and Possee, R.D., *The Baculovirus Expression System: A Laboratory Guide*, (Chapman & Hall, London); O'Reilly, D.R. *et al.*, *Baculovirus Expression Vectors: A Laboratory Manual* (Oxford University Press, New York, New York, 1994); and, Richardson, C. D., Ed., *Baculovirus Expression Protocols. Methods in Molecular Biology*, (Humana Press, Totowa, NJ 1995). Natural recombination within an insect cell will result in a recombinant baculovirus that contains coding sequences driven by the polyhedrin promoter. Recombinant viral stocks are made by methods commonly used in the art.

The second method of making recombinant baculovirus utilizes a transposon-based system described by Luckow, V.A., *et al.*, *J Virol* 67:4566 (1993). This system is sold in the Bac-to-Bac kit (Life Technologies, Rockville, MD). This system utilizes a transfer vector, pFastBac1™ (Life Technologies) containing a Tn7 transposon to move the DNA encoding the polypeptide into a baculovirus genome maintained in *E. coli* as a large plasmid called a "bacmid." The pFastBac1™ transfer vector utilizes the AcNPV polyhedrin promoter to drive the expression of the gene of interest. However, pFastBac1™ can be modified to a considerable degree. The polyhedrin promoter can be removed and substituted with the baculovirus basic protein promoter (also known as P_{cor}, p6.9 or MP promoter), which is expressed earlier in the baculovirus infection, and has been shown to be advantageous for expressing secreted proteins. See, Hill-Perkins, M.S. and Possee, R.D., *J Gen Virol* 71:971 (1990); Bonning, B.C. *et al.*, *J Gen Virol* 75:1551 (1994); and, Chazenbalk, G.D., and Rapoport, B., *J Biol Chem* 270:1543 (1995). In such transfer vector constructs, a short or long version of the basic protein promoter can be used. Moreover, transfer vectors can be constructed that replace the native secretory signal sequences with secretory signal sequences derived from insect proteins. For example, a secretory signal sequence from Ecdysteroid Glucosyltransferase (EGT), honey bee Melittin (Invitrogen, Carlsbad, CA), or baculovirus gp67 (PharMingen, San Diego, CA) can be used in constructs to replace the native secretory signal sequence. In addition, transfer vectors

can include an in-frame fusion with DNA encoding an epitope tag at the C- or N-terminus of the expressed polypeptide, for example, a Glu-Glu epitope tag, Grussenmeyer, T. *et al.*, *Proc Natl Acad Sci.* 82:7952 (1985). Using a technique known in the art, a transfer vector containing a recombinant gene is transformed into *E. coli*,
5 and screened for bacmids that contain an interrupted lacZ gene indicative of recombinant baculovirus. The bacmid DNA containing the recombinant baculovirus genome is isolated, using common techniques, and used to transfect *Spodoptera frugiperda* cells, *e.g.* Sf9 cells. Recombinant virus that expresses the polypeptide is subsequently produced. Recombinant viral stocks are made by methods commonly
10 used the art.

The recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda*. See, in general, Glick and Pasternak, *Molecular Biotechnology: Principles and Applications of Recombinant DNA* (ASM Press, Washington, D.C., 1994). Another suitable cell line is the High
15 FiveO™ cell line (Invitrogen) derived from *Trichoplusia ni* (U.S. Patent #5,300,435). Commercially available serum-free media are used to grow and maintain the cells. Suitable media are Sf900 II™ (Life Technologies) or ESF 921™ (Expression Systems) for the Sf9 cells; and Ex-cello405™ (JRH Biosciences, Lenexa, KS) or Express FiveO™ (Life Technologies) for the *T. ni* cells. The cells are grown up from an
20 inoculation density of approximately $2-5 \times 10^5$ cells to a density of $1-2 \times 10^6$ cells at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. The recombinant virus-infected cells typically produce the recombinant polypeptide at 12-72 hours post-infection and secrete it with varying efficiency into the medium. The culture is usually harvested 48 hours post-infection.
25 Centrifugation is used to separate the cells from the medium (supernatant). The supernatant containing the polypeptide is filtered through micropore filters, usually 0.45 μm pore size. Procedures used are generally described in available laboratory manuals (King, L. A. and Possee, R.D., *ibid.*, O'Reilly, D.R. *et al.*, *ibid.*; Richardson, C. D., *ibid.*). Subsequent purification of the polypeptide from the supernatant can be achieved
30 using methods described herein.

Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include *Saccharomyces cerevisiae*, *Pichia pastoris*, and *Pichia methanolica*. Methods for transforming *S. cerevisiae* cells with exogenous DNA and producing recombinant polypeptides
35 therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki *et al.*, U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch *et al.*, U.S. Patent No. 5,037,743; and Murray *et al.*, U.S. Patent No. 4,845,075.

Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in *Saccharomyces cerevisiae* is the *POT1* vector system disclosed by Kawasaki *et al.* (U.S. Patent No. 4,931,373), which
5 allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman *et al.*, U.S. Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and
10 4,661,454. Transformation systems for other yeasts, including *Hansenula polymorpha*, *Schizosaccharomyces pombe*, *Kluyveromyces lactis*, *Kluyveromyces fragilis*, *Ustilago maydis*, *Pichia pastoris*, *Pichia methanolica*, *Pichia guilliermondii* and *Candida maltosa* are known in the art. See, for example, Gleeson *et al.*, *J. Gen. Microbiol.* 132:3459 (1986) and Cregg, U.S. Patent No. 4,882,279. *Aspergillus* cells may be
15 utilized according to the methods of McKnight *et al.*, U.S. Patent No. 4,935,349. Methods for transforming *Acremonium chrysogenum* are disclosed by Sumino *et al.*, U.S. Patent No. 5,162,228. Methods for transforming *Neurospora* are disclosed by Lambowitz, U.S. Patent No. 4,486,533.

The use of *Pichia methanolica* as host for the production of recombinant
20 proteins is disclosed in WIPO Publications WO 97/17450, WO 97/17451, WO 98/02536, and WO 98/02565. DNA molecules for use in transforming *P. methanolica* will commonly be prepared as double-stranded, circular plasmids, which are preferably linearized prior to transformation. For polypeptide production in *P. methanolica*, it is preferred that the promoter and terminator in the plasmid be that of a *P. methanolica*
25 gene, such as a *P. methanolica* alcohol utilization gene (*AUG1* or *AUG2*). Other useful promoters include those of the dihydroxyacetone synthase (DHAS), formate dehydrogenase (FMD), and catalase (CAT) genes. To facilitate integration of the DNA into the host chromosome, it is preferred to have the entire expression segment of the plasmid flanked at both ends by host DNA sequences. A preferred selectable marker
30 for use in *Pichia methanolica* is a *P. methanolica* *ADE2* gene, which encodes phosphoribosyl-5-aminoimidazole carboxylase (AIRC; EC 4.1.1.21), which allows *ade2* host cells to grow in the absence of adenine. For large-scale, industrial processes where it is desirable to minimize the use of methanol, it is preferred to use host cells in which both methanol utilization genes (*AUG1* and *AUG2*) are deleted. For production
35 of secreted proteins, host cells deficient in vacuolar protease genes (*PEP4* and *PRB1*) are preferred. Electroporation is used to facilitate the introduction of a plasmid containing DNA encoding a polypeptide of interest into *P. methanolica* cells. It is

preferred to transform *P. methanolica* cells by electroporation using an exponentially decaying, pulsed electric field having a field strength of from 2.5 to 4.5 kV/cm, preferably about 3.75 kV/cm, and a time constant (t) of from 1 to 40 milliseconds, most preferably about 20 milliseconds.

5 Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art; see, e.g., Sambrook *et al.*, *ibid.*). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the
10 cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced
15 and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding.

20 Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and
25 minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient, which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell. *P. methanolica* cells are cultured in a medium comprising
30 adequate sources of carbon, nitrogen and trace nutrients at a temperature of about 25°C to 35°C. Liquid cultures are provided with sufficient aeration by conventional means, such as shaking of small flasks or sparging of fermentors. A preferred culture medium for *P. methanolica* is YEPD (2% D-glucose, 2% Bacto™ Peptone (Difco Laboratories, Detroit, MI), 1% Bacto™ yeast extract (Difco Laboratories), 0.004% adenine and
35 0.006% L-leucine).

Protein Isolation

It is preferred to purify the polypeptides of the present invention to $\geq 80\%$ purity, more preferably to $\geq 90\%$ purity, even more preferably $\geq 95\%$ purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide is

5 substantially free of other polypeptides, particularly other polypeptides of animal origin.

Expressed recombinant polypeptides (or chimeric polypeptides) can be purified using fractionation and/or conventional purification methods and media. Ammonium sulfate precipitation and acid or chaotrope extraction may be used for

10 fractionation of samples. Exemplary purification steps may include hydroxyapatite, size exclusion, FPLC and reverse-phase high performance liquid chromatography. Suitable chromatographic media include derivatized dextrans, agarose, cellulose, polyacrylamide, specialty silicas, and the like. PEI, DEAE, QAE and Q derivatives are preferred. Exemplary chromatographic media include those media derivatized with

15 phenyl, butyl, or octyl groups, such as Phenyl-Sepharose FF (Pharmacia), Toyopearl butyl 650 (Toso Haas, Montgomeryville, PA), Octyl-Sepharose (Pharmacia) and the like; or polyacrylic resins, such as Amberchrom CG 71 (Toso Haas) and the like. Suitable solid supports include glass beads, silica-based resins, cellulosic resins, agarose beads, cross-linked agarose beads, polystyrene beads, cross-linked

20 polyacrylamide resins and the like that are insoluble under the conditions in which they are to be used. These supports may be modified with reactive groups that allow attachment of proteins by amino groups, carboxyl groups, sulfhydryl groups, hydroxyl groups and/or carbohydrate moieties. Examples of coupling chemistries include cyanogen bromide activation, N-hydroxysuccinimide activation, epoxide activation,

25 sulfhydryl activation, hydrazide activation, and carboxyl and amino derivatives for carbodiimide coupling chemistries. These and other solid media are well known and widely used in the art, and are available from commercial suppliers. Methods for binding receptor polypeptides to support media are well known in the art. Selection of a particular method is a matter of routine design and is determined in part by the

30 properties of the chosen support. See, for example, *Affinity Chromatography: Principles & Methods* (Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988).

Polypeptides can be isolated by exploitation of their properties. For example, immobilized metal ion adsorption (IMAC) chromatography can be used to purify histidine-rich proteins, including those comprising polyhistidine tags. Briefly, a

35 gel is first charged with divalent metal ions to form a chelate, Sulkowski, *Trends in Biochem.* 3:1 (1985). Histidine-rich proteins will be adsorbed to this matrix with differing affinities, depending upon the metal ion used, and will be eluted by

competitive elution, lowering the pH, or use of strong chelating agents. Other methods of purification include purification of glycosylated proteins by lectin affinity chromatography and ion exchange chromatography. A protein fused to the Fc portion of an immunoglobulin can be purified using a 'Protein A column'. *Methods in Enzymol.*,
5 Vol. 182, "Guide to Protein Purification", M. Deutscher, (ed.), page 529-539 (Acad. Press, San Diego, 1990). Within additional embodiments of the invention, a fusion of the polypeptide of interest and an affinity tag (*e.g.*, maltose-binding protein, an immunoglobulin domain) may be constructed to facilitate purification.

As used herein, the term "antibodies" includes polyclonal antibodies,
10 affinity-purified polyclonal antibodies, monoclonal antibodies, and antigen-binding fragments, such as F(ab')₂ and Fab proteolytic fragments. Genetically engineered intact antibodies or fragments, such as chimeric antibodies, Fv fragments, single chain antibodies and the like, as well as synthetic antigen-binding peptides and polypeptides, are also included. Non-human antibodies may be humanized by grafting non-human
15 CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through
20 humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that bind to protein or peptide. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.) (Cold Spring
25 Harbor Laboratory Press, 1988). Representative examples of such assays include: concurrent immunoelectrophoresis, radioimmunoassay, radioimmuno-precipitation, enzyme-linked immunosorbent assay (ELISA), dot blot or Western blot assay, inhibition or competition assay, and sandwich assay.

The soluble receptors of the present invention can be used to down-
30 regulate IL-20, which has been shown to be involved in a number of inflammatory processes. Specifically, IL-20 has been shown to up-regulate IL-8. Inflammatory diseases in which IL-8 plays a significant role, and for which a decrease in IL-8 would be beneficial are, adult respiratory disease (ARD), septic shock, multiple organ failure, inflammatory lung injury such as asthma or bronchitis, bacterial pneumonia, psoriasis,
35 eczema, atopic and contact dermatitis, and inflammatory bowel disease such as ulcerative colitis and Crohn's disease. Thus, the soluble receptor to IL-20 of the present invention can be administered to a patient to treat these diseases.

Biology of IL-20, Its receptor and Its Role in Psoriasis

Two orphan class II cytokine receptors, both of which are expressed in skin, were identified as IL-20 receptor subunits. Both IL-20 receptor subunits are
5 required for ligand binding, distinguishing their role from that of subunits in the four other known class II cytokine receptors. IL-22R and IL-20RB are also coexpressed in a number of human tissues besides skin, including ovary, adrenal gland, testis, salivary gland, muscle, lung, kidney, heart and to a lesser degree the small intestine suggesting additional target tissues for IL-20 action. We conclude that the IL-20 heterodimeric
10 receptor is structurally similar to other class II cytokine receptors and is expressed in skin where we have demonstrated activity of the IL-20 ligand.

Two lines of evidence indicate that a role IL-20 and its receptor are involved in psoriasis. This multigenic skin disease is characterized by increased keratinocyte proliferation, altered keratinocyte differentiation, and infiltration of
15 immune cells into the skin. The first line of evidence for a role of IL-20 in psoriasis is that the observed hyperkeratosis and thickened epidermis in the transgenic mice that resemble human psoriatic abnormalities. Decreased numbers of tonofilaments, thought to be related to defective keratinization, are a striking feature of human psoriasis. Intramitochondrial inclusions have been found in both chemically induced and naturally
20 occurring hyperplastic skin conditions in mice. The cause of the inclusions and their effects on mitochondrial function, if any, are unknown. We conclude that IL-20 transgenic mice exhibit many of the characteristics observed in human psoriasis.

Use of Antagonist to IL-20 to Treat Psoriasis

25 As indicated in the discussion above and the examples below, IL-20 is involved in the pathology of psoriasis. Thus, the soluble receptors of the present invention can be administered to an individual to down-regulate IL-20 and thus treat psoriasis.

Psoriasis is one of the most common dermatologic diseases, affecting up
30 to 1 to 2 percent of the world's population. It is a chronic inflammatory skin disorder characterized by erythematous, sharply demarcated papules and rounded plaques,

covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic. Traumatized areas often develop lesions of psoriasis. Additionally, other external factors may exacerbate psoriasis including infections, stress, and medications, *e.g.* lithium, beta blockers, and anti-malarials.

5 The most common variety of psoriasis is called plaque type. Patients with plaque-type psoriasis will have stable, slowly growing plaques, which remain basically unchanged for long periods of time. The most common areas for plaque psoriasis to occur are the elbows knees, gluteal cleft, and the scalp. Involvement tends to be symmetrical. Inverse psoriasis affects the intertriginous regions including the
10 axilla, groin, submammary region, and navel, and it also tends to affect the scalp, palms, and soles. The individual lesions are sharply demarcated plaques but may be moist due to their location. Plaque-type psoriasis generally develops slowly and runs an indolent course. It rarely spontaneously remits.

 Eruptive psoriasis (guttate psoriasis) is most common in children and
15 young adults. It develops acutely in individuals without psoriasis or in those with chronic plaque psoriasis. Patients present with many small erythematous, scaling papules, frequently after upper respiratory tract infection with beta-hemolytic streptococci. Patients with psoriasis may also develop pustular lesions. These may be localized to the palms and soles or may be generalized and associated with fever,
20 malaise, diarrhea, and arthralgias..

 About half of all patients with psoriasis have fingernail involvement, appearing as punctate pitting, nail thickening or subungual hyperkeratosis. About 5 to 10 percent of patients with psoriasis have associated joint complaints, and these are most often found in patients with fingernail involvement. Although some have the
25 coincident occurrence of classic rheumatoid arthritis, many have joint disease that falls into one of five type associated with psoriasis: (1) disease limited to a single or a few small joints (70 percent of cases); (2) a seronegative rheumatoid arthritis-like disease; (3) involvement of the distal interphalangeal joints; (4) severe destructive arthritis with the development
30 of "arthritis mutilans"; and (5) disease limited to the spine.

Psoriasis can be treated by administering antagonists to IL-20. The preferred antagonists are either a soluble receptor to IL-20 or antibodies, antibody fragments or single chain antibodies that bind to either the IL-20 receptor or to IL-20. The antagonists to IL-20 can be administered alone or in combination with other
5 established therapies such as lubricants, keratolytics, topical corticosteroids, topical vitamin D derivatives, anthralin, systemic antimetabolites such as methotrexate, psoralen-ultraviolet-light therapy (PUVA), etretinate, isotretinoin, cyclosporine, and the topical vitamin D3 derivative calcipotriol. The antagonists, in particularly the soluble receptor or the antibodies that bind to IL-20 or the IL-20 receptor can be administered
10 to individual subcutaneously, intravenously, or transdermally using a cream or transdermal patch that contains the antagonist of IL-20. If administered subcutaneously, the antagonist can be injected into one or more psoriatic plaques. If administered transdermally, the antagonists can be administered directly on the plaques using a cream containing the antagonist to IL-20.

15

Use of Antagonists to IL-20 to Treat Inflammatory Conditions of the Lung.

A soluble receptor of IL-20 of the present invention can be administered to a person who has asthma, bronchitis or cystic fibrosis or other inflammatory lung disease to treat the disease. The antagonists can be administered by any suitable method
20 including intravenous, subcutaneous, bronchial lavage, and the use of inhalant containing an antagonist to IL-20.

Administration of the IL-20 Soluble Receptor

The quantities of the IL-20 soluble necessary for effective therapy will depend upon many different factors, including means of administration, target site,
25 physiological state of the patient, and other medications administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in vivo* administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Methods for administration
30 include oral, intravenous, peritoneal, intramuscular, transdermal or administration into the lung or trachea in spray form by means of a nebulizer or atomizer. Pharmaceutically

- acceptable carriers will include water, saline, buffers to name just a few. Dosage ranges would ordinarily be expected from 1 μ g to 1000 μ g per kilogram of body weight per day. A dosage for an average adult of the IL-20 soluble receptor would be about 25 mg given twice weekly as a subcutaneous injection. Injections could be given at the site of psoriatic lesions for the treatment of psoriasis. For subcutaneous or intravenous administration of the antagonist to IL-20, the antibody or soluble receptor can be in phosphate buffered saline. Also in skin diseases such as psoriasis, the antagonist to IL-20 can be administered via an ointment or transdermal patch. The doses by may be higher or lower as can be determined by a medical doctor with ordinary skill in the art.
- For a complete discussion of drug formulations and dosage ranges see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Co., Easton, Penn., 1996), and *Goodman and Gilman's: The Pharmacological Bases of Therapeutics*, 9th Ed. (Pergamon Press 1996).

- The invention is further illustrated by the following non-limiting examples:

Example 1

Up-regulation of IL-8 by IL-20

Methods:

- Normal Human Epidermal neonatal keratinocytes (NHEK) (from Clonetics) at passage 2 were plated and grown to confluency in 12 well tissue culture plates. KGM (Keratinocyte growth media) was purchased from Clonetics. When cells reached confluency, they were washed with KGM media minus growth factors = KBM (keratinocyte basal media). Cells were serum starved in KBM for 72 hours prior to the addition of test compounds. Thrombin at 1 I.U./mL and trypsin at 25nM were used as positive controls. One mL of media/well was added. KBM only was used as the negative control.

- IL-20 was made up in KBM media and added at varying concentrations, from 2.5 μ g/ml down to 618ng/mL in a first experiment and from 2.5 μ g/mL down to 3ng/mL in a second experiment.

Cells were incubated at 37° C, 5% CO₂ for 48 hours. Supernatants were removed and frozen at -80° C for several days prior to assaying for IL-8 and GM-CSF

levels. Human IL-8 Immunoassay kit # D8050 (RandD Systems, Inc.) and human GM-CSF Immunoassay kit # HSGMO (RandD Systems, Inc.) were used to determine cytokine production following manufacturer's instructions.

5 Results

The results indicated that the expression of IL-8 and GM-CSF were induced by IL-20.

Example 2

10 Cloning of IL-20RB

Cloning of IL-20RB coding region

Two PCR primers were designed based on the sequence from International Patent Application No. PCT/US99/03735 (publication no. WO 99/46379) filed on March 8, 1999. SEQ ID NO: 38 contains the ATG (Met1) codon with an EcoRI restriction site, SEQ ID NO: 37 contains the stop codon (TAG) with an XhoI restriction site. The PCR amplification was carried out using a human keratinocyte (HaCaT) cDNA library DNA as a template and SEQ ID NO: 37 and SEQ ID NO: 38 as primers. The PCR reaction was performed as follows: incubation at 94°C for 1 min followed by 20 30 cycles of 94°C for 30 sec and 68°C for 2 min, after additional 68°C for 4 min, the reaction was stored at 4°C. The PCR products were run on 1% Agarose gel, and a 1 kb DNA band was observed. The PCR products were cut from the gel and the DNA was purified using a QIAquick Gel Extraction Kit (Qiagen). The purified DNA was digested with EcoRI and XhoI, and cloned into a pZP vector that was called pZP7N. A pZP 25 plasmid is a mammalian expression vector containing an expression cassette having the mouse metallothionein-1 promoter, human tPA leader peptide, multiple restriction sites for insertion of coding sequences, a Glu-Glu tag, and a human growth hormone terminator. The plasmid also has an E. coli origin of replication, a mammalian selectable marker expression unit having an SV40 promoter, an enhancer and an origin 30 of replication, as well as a DHFR gene, and the SV40 terminator. Several IL-20RB-pZP7N clones were sequenced. They all contain three non-conservative mutations

compared with the sequence of IL-20RB in PCT/US99/03735: (sequence IL-20RB-pZP7N), 146 Pro (CCC) -- Thr (ACC), 148 His (CAT) -- Asp (GAT), and 171 Thr (ACG) -- Arg (AGG).

To verify the three substitutions in IL-20RB-pZP7N clone, PCR
5 amplification was carried out using three difference cDNA sources -- fetal skin
marathon cDNA, HaCaT cDNA library DNA, and prostate smooth muscle cDNA
library DNA -- as templates. The PCR products were gel purified and sequenced. The
sequence of each of the three PCR products was consistent with that of the IL-20RB-
pZP7N clone. IL-20RB is SEQ ID NO: 22 and 23, and the mature extracellular domain
10 is SEQ ID NO: 21.

Example 3

Binding of IL-20 to IL-20RB/ IL-22R Heterodimer

15 A cell-based binding assay was used to verify IL-20 binds to IL-22R- IL-
20RB heterodimer.

Expression vectors containing known and orphan Class II cytokine
receptors (including IL-22R and IL-20RB) were transiently transfected into Baf3 cells.

Plated cells out at 5000cells/well, treated cells with IL-20 (zcyto10),
20 MDA-7, and Soluble Proteins.
-Inc. at 37 degrees for 3 days (72hrs.)
-Added 20ul/well of Alamar Blue, inc. at 37 degrees overnight (24 hrs.)
-Read on the f-Max (Molecular Devises) in the Robotics room on 544 excitation/ 590
emission setting.

25

Results:

-Positive proliferative response with treatments of IL-20 (zcyto10) and MDA-7 from
0.1ng/ml to 100ng/ml on Baf3/DIRS1/cytoR11 cell line.
-A neutralization of the positive proliferative response of IL-20 and MDA-7 (same
30 conc.'s) when IL-20 and MDA-7 were treated in combination with the IL-22R Soluble
Receptor (heterodimeric Sol. R.) at a 60 fold molar excess.

-A neutralization of the positive proliferative response of MDA-7 (from 0.1 to 10ng/ml) when MDA-7 was treated in combination with IL-20RB Soluble Protein (thrombin cleaved version) at a 60 fold molar excess.

5

Example 4

Up-regulation of Inflammatory Cytokines by IL-20

Cell Treatment

The human keratinocyte cell line, HaCaT was grown at 37°C to several days post-confluence in T-75 tissue culture flasks. At this point, normal growth media
10 (DMEM + 10% FBS) was removed and replaced with serum-free media. Cells were then incubated for two days at 37°C. DMEM was then removed and four flasks of cells per treatment were treated with one of each of the following conditions for four hours at 37°C: recombinant human (rh) IL-1 alpha at 5 ng/mL, rh IL-1 alpha at 20 ng/mL, rh IL-1 alpha at 5 ng/mL + IL-20 at 1µg/mL, IL-20 at 1µg/mL, or rh IL-10 at 10 ng/mL.

15

RNA Isolation

Following cytokine treatment, media was removed and cells were lysed using a guanidium thiocyanate solution. Total RNA was isolated from the cell lysate by an overnight spin on a cesium chloride gradient. The following day, the RNA pellet
20 was resuspended in a TE/SDS solution and ethanol precipitated. RNA was then quantitated using a spectrophotometer, followed by a DNase treatment as per Section V.B. of Clontech's Atlas™ cDNA Expression Arrays User Manual (version PT3140-1/PR9X390, published 11/5/99). Quality of RNA samples was verified by purity calculations based on spec readings, and by visualization on agarose gel. Genomic
25 contamination of the RNA samples was ruled out by PCR analysis of the beta-actin gene.

Clontech's protocols for polyA+ enrichment, probe synthesis and hybridization to Atlas™ arrays were followed (see above, plus Atlas™ Pure Total RNA Labeling System User Manual, PT3231-1/PR96157, published 6/22/99). Briefly,
30 polyA+ RNA was isolated from 50 mg of total RNA using streptavidin coated magnetic beads (by Clontech, Paolo Alto, CA) and a magnetic particle separator. PolyA+ RNA

was then labeled with $\alpha^{32}\text{P}$ -dATP via RT-PCR. Clontech CDS primers specific to the 268 genes on the AtlasTM human cytokine/receptor array (Cat. #7744-1) were used in the reaction. Labeled probe was isolated using column chromatography and counted in scintillation fluid.

5

Array membrane Hybridization

AtlasTM arrays were pre-hybridized with Clontech ExpressHyb plus 100 mg/mL heat denatured salmon sperm DNA for at least thirty minutes at 68°C with continuous agitation. Membranes were then hybridized with 1.9×10^6 CPM/mL (a total of 1.14×10^7 CPM) overnight at 68°C with continuous agitation. The following day, membranes were washed for thirty minutes x 4 in 2X SSC, 1% SDS at 68°C, plus for thirty minutes x 1 in 0.1X SSC, 0.5% SDS at 68°C, followed by one final room temperature wash for five minutes in 2X SSC. Array membranes were then placed in Kodak plastic pouches sealed and exposed to a phosphor imager screen overnight at room temperature. The next day, phosphor screens were scanned on a phosphor imager and analyzed using Clontech's AtlasImageTM 1.0 software.

10

15

Results

Genes Up-regulated by IL-20

- 20 1. Tumor necrosis factor (TNF) was up-regulated 1.9-2.4 fold by IL-20.
2. Placental growth factors 1 & 2 (PLGF) were up-regulated 1.9-2.0 fold by IL-20.
3. Coagulating factor II receptor was up-regulated 2.0-2.5 fold by IL-20.
4. Calcitonin receptor was up-regulated 2.2-2.3 fold by IL-20.
5. TNF-inducible hyaluronate-binding protein TSG-6 was up-regulated 2.1-2.2
- 25 fold by IL-20.
6. Vascular endothelial growth factor (VEGF) receptor-1 precursor, tyrosine-protein kinase receptor (FLT-1) (SFLT) was up-regulated 2.1-2.7 fold by IL-20.
7. MRP-8 (calcium binding protein in macrophages MIF-related) was up-regulated 2.9-4.1 fold by IL-20.
- 30 8. MRP-14 (calcium binding protein in macrophages MIF-related) was up-regulated 3.0-3.8 fold by IL-20.

9. Relaxin H2 was up-regulated 3.14 fold by IL-20.
10. Transforming growth factor beta (TGF β) receptor III 300 kDa was up-regulated 2.4-3.6 fold by IL-20.

5 Genes Showing Synergy with IL-20 + IL-1 Treatment

1. Bone morphogenic protein 2a was up-regulated 1.8 fold with IL-20 treatment alone, 2.5 fold with IL-1 treatment alone, and 8.2 fold with both IL-20 and IL-1 treatment together.
2. MRP-8 was up-regulated 2.9 fold with IL-20 treatment alone, 10.7 fold with IL-1 treatment alone and 18.0 fold with both IL-20 and IL-1 treatment together.
3. Erythroid differentiation protein (EDF) was up-regulated 1.9 fold with IL-20 treatment alone, 9.7 fold with IL-1 treatment alone and 19.0 fold with both IL-20 and IL-1 treatment together.
4. MRP-14 (calcium binding protein in macrophages, MIF related) was up-regulated 3.0 fold with IL-20 treatment alone, 12.2 fold with IL-1 treatment alone and 20.3 fold with both IL-20 and IL-1 treatment together.
5. Heparin-binding EGF-like growth factor was up-regulated 2.0 fold with IL-20 treatment alone, 14 fold with IL-1 treatment alone and 25.0 fold with both IL-20 and IL-1 treatment together.
6. Beta-thromboglobulin-like protein was up-regulated 1.5 fold with IL-20 treatment alone, 15 fold with IL-1 treatment alone and 27 fold with both IL-20 and IL-1 treatment together.
7. Brain-derived neurotrophic factor (BDNF) was up-regulated 1.7 fold with IL-20 treatment alone, 25 fold with IL-1 treatment alone and 48 fold with both IL-20 and IL-1 treatment together.
8. Monocyte chemotactic and activating factor MCAF was up-regulated 1.3 fold with IL-20 treatment alone, 32 fold with IL-1 treatment alone and 56 fold with both IL-20 and IL-1 treatment together.

Example 5

IL-20 Transgenic Phenotype

Both human and mouse IL-20 were overexpressed in transgenic mice using a variety of promoters. The liver-specific mouse albumin promoter, directing
5 expression of human IL-20, was used initially in an attempt to achieve circulating levels of protein. Subsequent studies were conducted using the keratin 14 (K14) promoter, which primarily targets expression to the epidermis and other stratified squamous epithelia; the mouse metallothionein-1 promoter, which gives a broad expression pattern; and the E μ LCK promoter, which drives expression in cells of the lymphoid
10 lineage. Similar results were obtained in all four cases, possibly because these promoters all give rise to circulating levels of IL-20.

In all cases, transgenic pups expressing the IL-20 transgene were smaller than non-transgenic littermates, had a shiny appearance with tight, wrinkled skin and died within the first few days after birth. Pups had milk in their stomachs indicating
15 that they were able to suckle. These mice had swollen extremities, tail, nostril and mouth regions and had difficulty moving. In addition, the mice were frail, lacked visible adipose tissue and had delayed ear and toe development. Low expression levels in liver (less than 100 mRNA molecules/cell) were sufficient for both the neonatal lethality and skin abnormalities. Transgenic mice without a visible phenotype either
20 did not express the transgene, did not express it at detectable levels, or were mosaic.

Histologic analysis of the skin of the IL-20 transgenic mice showed a thickened epidermis, hyperkeratosis and a compact stratum corneum compared to non-transgenic littermates. Serocellular crusts (scabs) were observed occasionally. Electron
microscopic (EM) analysis of skin from transgenic mice showed intramitochondrial
25 lipoid inclusions, mottled keratohyaline granules, and relatively few tonofilaments similar to that observed in human psoriatic skin and in mouse skin disease models. In addition, many of the transgenic mice had apoptotic thymic lymphocytes. No other abnormalities were detected by histopathological analysis. These histological and EM results support and extend the observed gross skin alterations.

Example 6

Experimental Procedures:

Luciferase Assay

- Luciferase reporter assays were performed using BHK cells stably
- 5 transfected with IL-22R and IL-20RB and utilizing the STAT-driven luciferase reporter cassette. Cells were switched to serum-free medium overnight prior to treatment with serial dilutions of IL-19, IL-20, and MDA-7 in the presence or absence of IL-20RA/IL-20RB soluble receptor. Cells were lysed and read on the Berthold MicroLumat Plus for luciferase reporter activity.

BaF3 Proliferation Assay

Proliferation assays used Alamar Blue, which was added to the cells 24 h prior to being read on a *f*max plate reader (Molecular Devices, Sunnyvale, CA) using the Softmax Pro program.

RT-PCR Analysis on Human Tissues

RT-PCR was performed on a human Rapid-Scan gene expression panel (Origene Technologies, Inc.) using primers 5'-ccccagacacgggtctacagcat-3' and 5'-gggtcaggccgaagaactcatat-3' to amplify a 440 bp fragment of human *IL22R*. PCR conditions are 94°C for 2 min., followed by 35 cycles of 94°C for 15 sec., 72°C for 90 sec, then a final extension step of 72°C for 2 min.

Results:

Since *IL-22R* is a shared alpha subunit, we evaluated an Origene panel for the expression of *IL-22R* mRNA. The highest *IL-22R* expression was detected in the pancreas, with skin and lung also exhibiting strong expression.

To test the possibility that the *IL-20* subfamily might activate other Class II receptor combinations, BaF3 cells were stably transfected with Class II receptor subunits alone or in combinations and treated with the ligands. The assay shows that both *IL-20* and *MDA-7* stimulate an additional receptor complex consisting of consisting of *IL-22R/IL-20RB* (Table 1). We next wanted to determine which soluble receptors could block ligand activity. As mentioned above, *IL-20RA/IL-20RB* heterodimeric soluble receptor blocked proliferation stimulated by *IL-20*, *IL-19*, and *MDA-7*. In addition, *IL-20RB* soluble receptor alone blocked the activity of *IL-19* and *MDA-7*, but not *IL-20*.

Since *IL-22R* is a shared alpha subunit, we evaluated an Origene panel for the expression of *IL-22R* mRNA (Table 2). The highest expression was detected in the pancreas, with skin and lung also exhibiting strong expression. Thus, overall *IL-20Rα*, *IL-20Rβ*, and *IL-22R* all have robust expression in skin and lung.

Since *IL-20R α* , *IL-20R β* , and *IL-22R* are all expressed in the lung, we used *in situ* hybridization to evaluate whether the same cell types expressed all three receptors. Figure 3 shows that both epithelial cells as well as immune infiltrates exhibit positive staining in lung sections tested for mRNA expression by *in situ* hybridization.

WHAT IS CLAIMED IS:

1. An isolated soluble receptor comprised of an IL-22R subunit and a IL-20RB subunit, wherein the IL-22R subunit is comprised of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 13, 25, 26 31 and 32, and the IL-20B subunit is comprised of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15-21,23, 28, 29, 34 and 35.
2. The soluble receptor of claim 1 wherein the IL-22R subunit and the IL-20B subunit are linked together by a polypeptide linker.
3. The soluble receptor of claim 2 wherein the polypeptide linker has about 100 to 240 amino acid residues.
4. The soluble receptor of claim 3 wherein the polypeptide linker has about 170 amino acid residues.
5. The soluble receptor of claim 1 wherein the IL-22R subunit and the IL-20B subunit each have a polypeptide linker fused to the subunit, and each of the polypeptide linkers has at least one cysteine residue, wherein at least one disulfide bond forms with a cysteine from the polypeptide linker of the IL-22R subunit and with a cysteine from the polypeptide linker of the IL-20B subunit.
6. The soluble receptor of claim 5 wherein the IL-22R subunit is fused to all or a portion of the constant region of a heavy chain of an immunoglobulin (Ig) molecule, and the IL-20B subunit is fused to all or a portion of the constant region of a light chain of an immunoglobulin molecule, wherein the light chain and the heavy chain are disulfide bonded together.

7. The soluble receptor of claim 6 wherein the constant region of the heavy chain is comprised of a CH1 domain, a CH2 domain and a hinge sequence that connects the CH1 domain with the CH2 domain.
8. The soluble receptor of claim 6 wherein the IL-22R subunit fused to the constant region of the heavy chain is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 25, 26, 31 and 32, and the IL-20B subunit fused to the constant region of the light chain of the Ig molecule is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 29, 34 and 35.
9. The soluble receptor of claim 5 wherein the IL-20B subunit is fused to all or a portion of the constant region of a heavy chain of an Ig molecule, and the IL-22R subunit is fused to all or a portion of the constant region of a light chain of an immunoglobulin molecule, wherein the light chain and the heavy chain are disulfide bonded together.
10. A for producing a soluble receptor comprised of extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised a DNA sequence that encodes the extracellular portion of IL-22R and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a DNA sequence that encodes the extracellular portion of IL-20RB and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow production of a fusion protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the polypeptide from the host cell.
11. A method for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of DNA that encodes the extracellular portion of IL-20RB and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell

a second DNA construct comprised of a DNA sequence that encodes the extracellular portion of IL-22R and a DNA sequence that encodes an immunoglobulin heavy chain constant region (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the production of a dimerized heterodimeric fusion protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the dimerized polypeptide from the host cell.

12. A method for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a DNA construct containing a DNA construct that encodes the extracellular portion of IL-20RB and a DNA construct of the extracellular portion of IL-22R, (b) growing the host cell in an appropriate medium under physiological conditions to allow the production of the extracellular domain of IL-22R and the extracellular domain of IL-20RB; and (d) isolating the polypeptides from the host cell.

13. A host cells transformed or transfected with a DNA construct that encodes the extracellular domain of IL-22RB and a DNA construct that encodes the extracellular domain of IL-20RB.

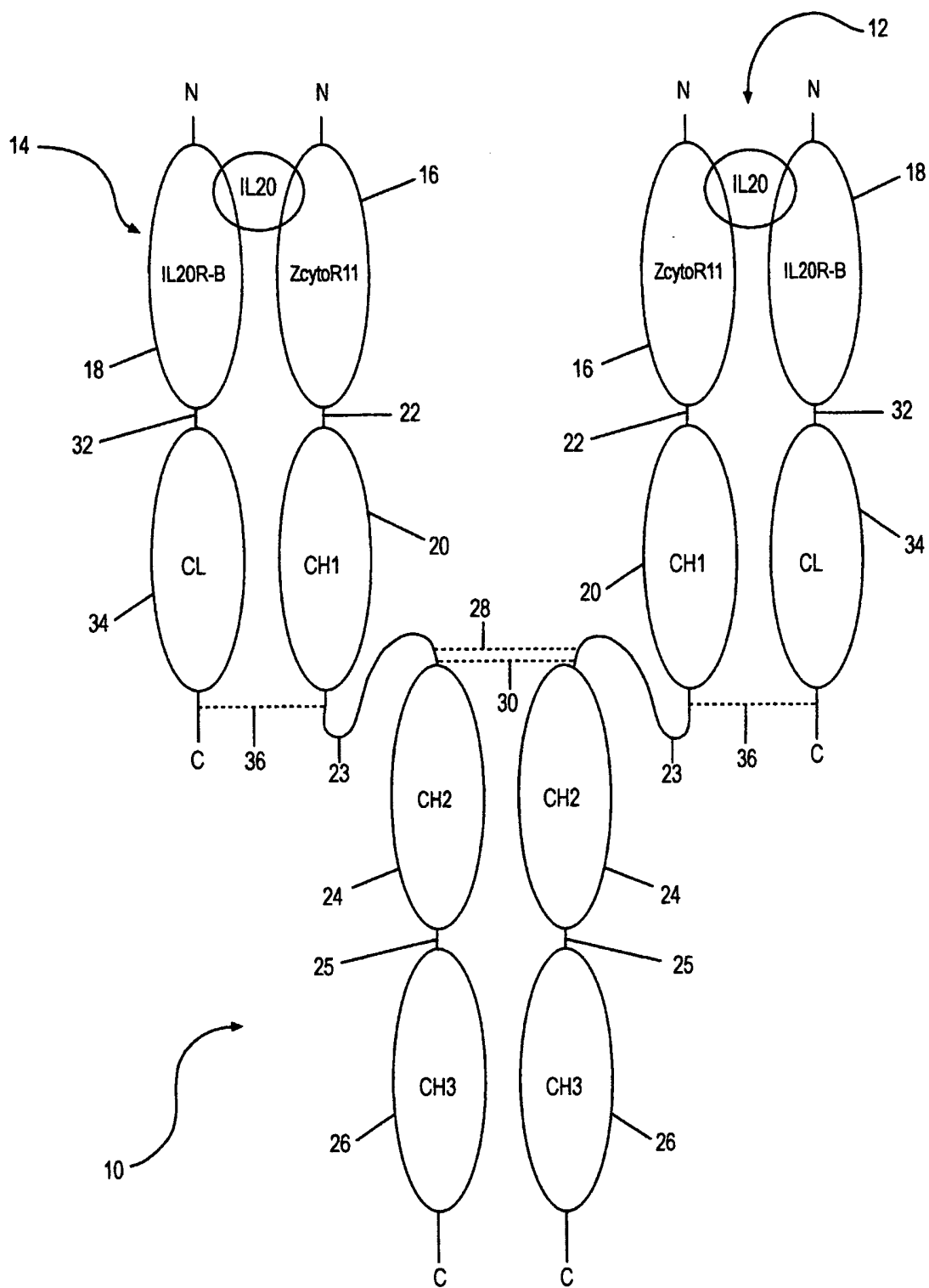


FIG.1

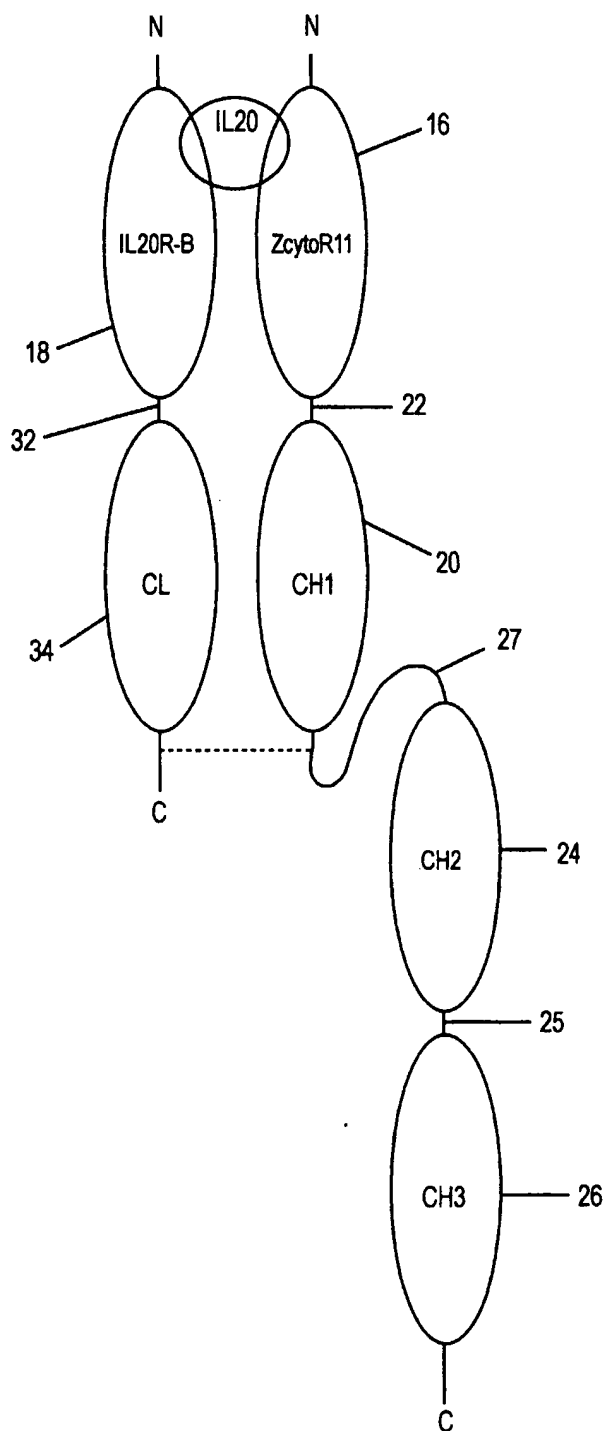


FIG.2

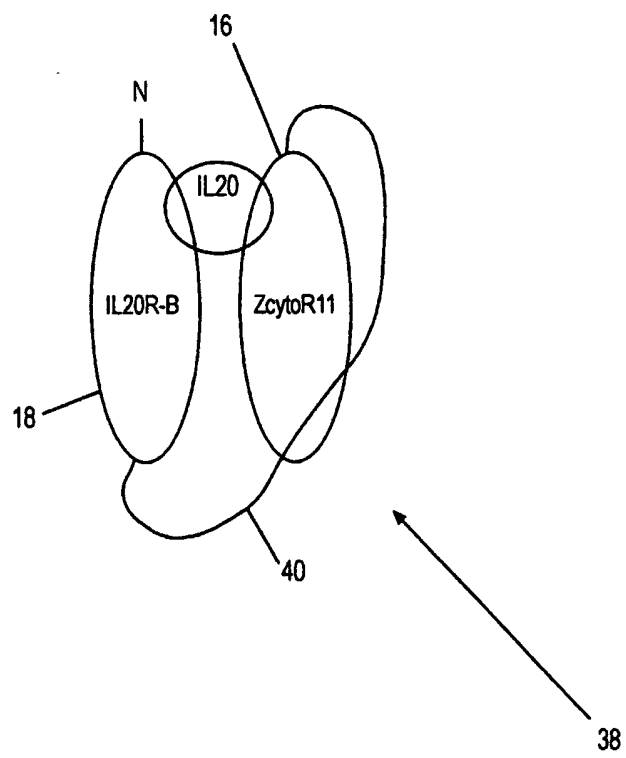


FIG.3

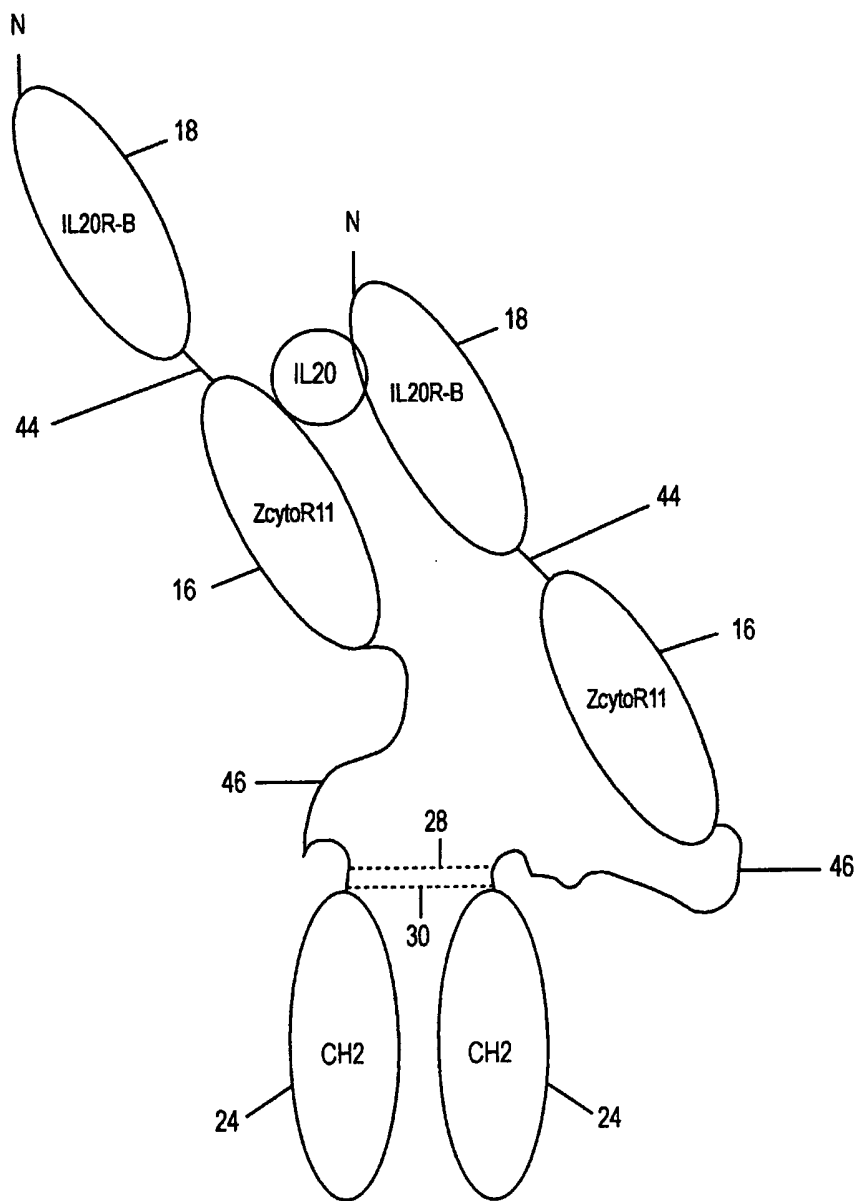


FIG.5

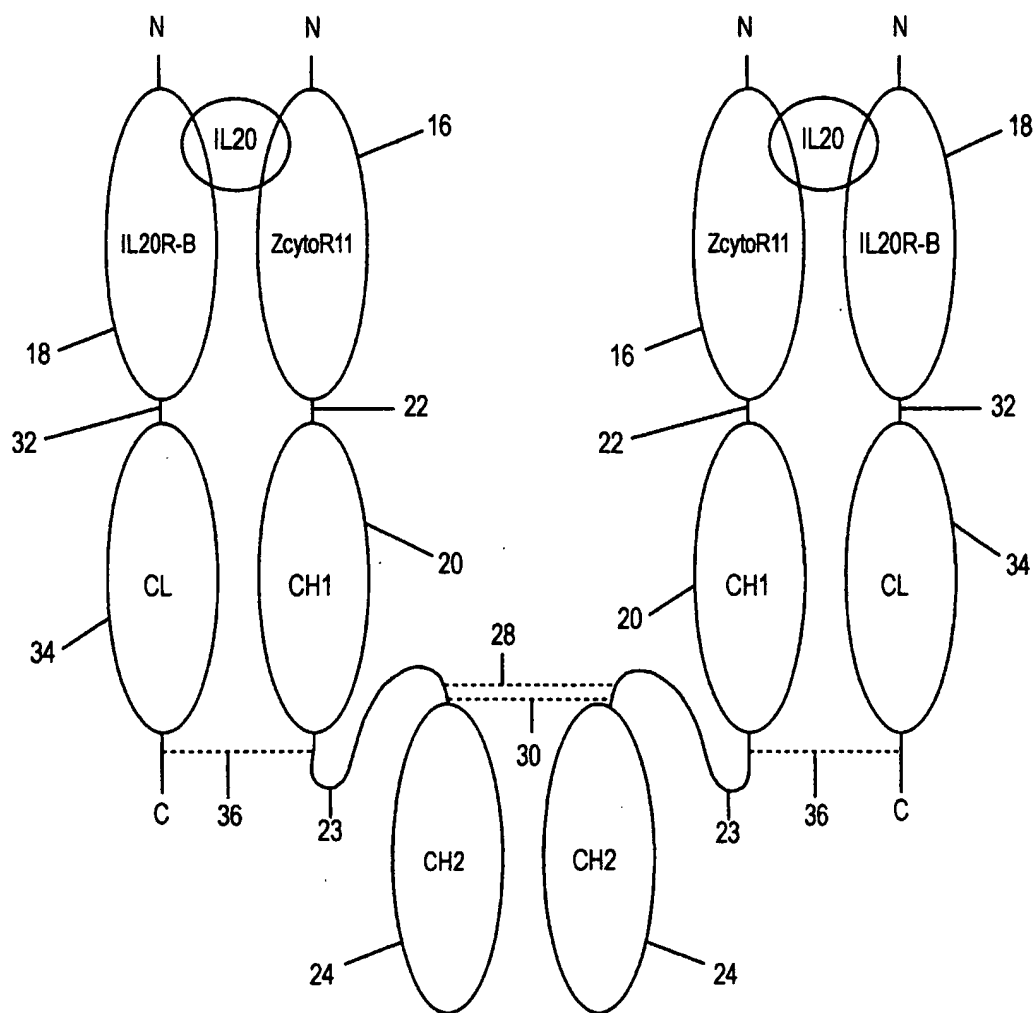


FIG.6

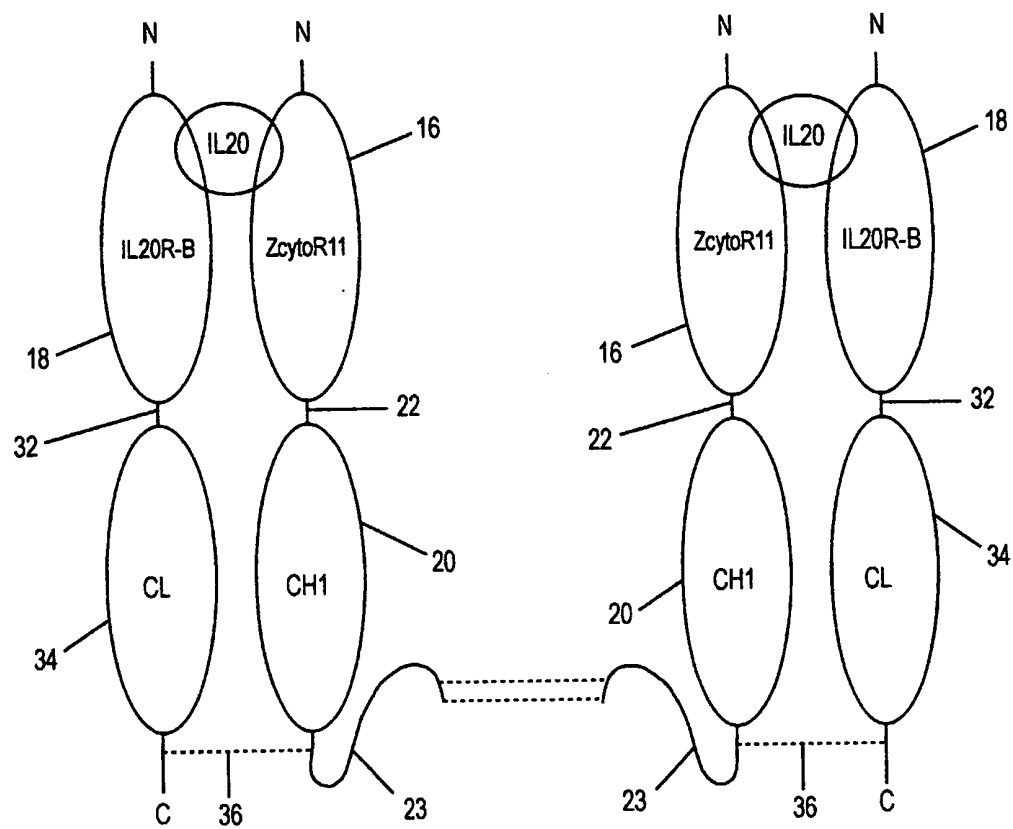


FIG.7

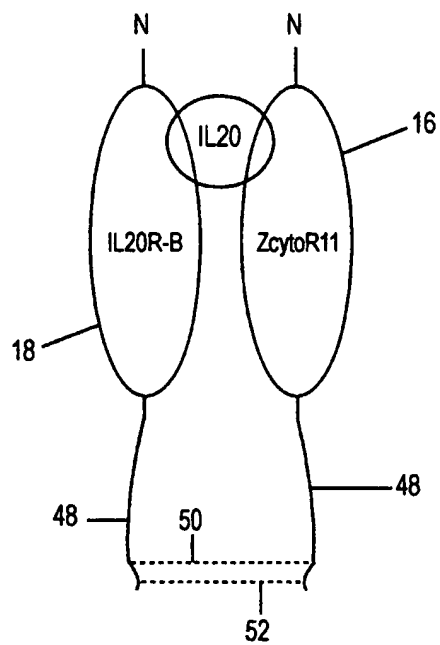


FIG.8

SEQUENCE LISTING

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 Foster, Donald C.
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 Leu Leu Trp Thr Pro Leu Thr Gly Leu Lys Thr Leu His Leu Gly Ser
 20 25 30
 Cys Val Ile Thr Ala Asn Leu Gln Ala Ile Gln Lys Glu Phe Ser Glu
 35 40 45
 Ile Arg Asp Ser Val Gln Ala Glu Asp Thr Asn Ile Asp Ile Arg Ile
 50 55 60
 Leu Arg Thr Thr Glu Ser Leu Lys Asp Ile Lys Ser Leu Asp Arg Cys
 65 70 75 80
 Cys Phe Leu Arg His Leu Val Arg Phe Tyr Leu Asp Arg Val Phe Lys
 85 90 95
 Val Tyr Gln Thr Pro Asp His His Thr Leu Arg Lys Ile Ser Ser Leu
 100 105 110
 Ala Asn Ser Phe Leu Ile Ile Lys Lys Asp Leu Ser Val Cys His Ser
 115 120 125
 His Met Ala Cys His Cys Gly Glu Glu Ala Met Glu Lys Tyr Asn Gln
 130 135 140
 Ile Leu Ser His Phe Ile Glu Leu Glu Leu Gln Ala Ala Val Val Lys
 145 150 155 160
 Ala Leu Gly Glu Leu Gly Ile Leu Leu Arg Trp Met Glu Glu Met Leu
 165 170 175

<210> 6
 <211> 152
 <212> PRT
 <213> Mouse

<400> 6
 Leu Lys Thr Leu His Leu Gly Ser Cys Val Ile Thr Ala Asn Leu Gln
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 Ala Ile Gln Lys Glu Phe Ser Glu Ile Arg Asp Ser Val Gln Ala Glu
 20 25 30
 Asp Thr Asn Ile Asp Ile Arg Ile Leu Arg Thr Thr Glu Ser Leu Lys
 35 40 45
 Asp Ile Lys Ser Leu Asp Arg Cys Cys Phe Leu Arg His Leu Val Arg
 50 55 60
 Phe Tyr Leu Asp Arg Val Phe Lys Val Tyr Gln Thr Pro Asp His His
 65 70 75 80
 Thr Leu Arg Lys Ile Ser Ser Leu Ala Asn Ser Phe Leu Ile Ile Lys
 85 90 95
 Lys Asp Leu Ser Val Cys His Ser His Met Ala Cys His Cys Gly Glu
 100 105 110
 Glu Ala Met Glu Lys Tyr Asn Gln Ile Leu Ser His Phe Ile Glu Leu
 115 120 125
 Glu Leu Gln Ala Ala Val Val Lys Ala Leu Gly Glu Leu Gly Ile Leu
 130 135 140
 Leu Arg Trp Met Glu Glu Met Leu
 145 150

<210> 7
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<400> 7
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 20 25 30
 Leu Arg Thr Thr Glu Ser Leu Lys Asp Ile Lys Ser Leu Asp Arg Cys
 35 40 45
 Cys Phe Leu Arg His Leu Val Arg Phe Tyr Leu Asp Arg Val Phe Lys
 50 55 60
 Val Tyr Gln Thr Pro Asp His His Thr Leu Arg Lys Ile Ser Ser Leu
 65 70 75 80
 Ala Asn Ser Phe Leu Ile Ile Lys Lys Asp Leu Ser Val Cys His Ser
 85 90 95
 His Met Ala Cys His Cys Gly Glu Glu Ala Met Glu Lys Tyr Asn Gln
 100 105 110
 Ile Leu Ser His Phe Ile Glu Leu Glu Leu Gln Ala Ala Val Val Lys
 115 120 125
 Ala Leu Gly Glu Leu Gly Ile Leu Leu Arg Trp Met Glu Glu Met Leu
 130 135 140

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 <211> 154
 <212> PRT
 <213> Homo sapiens

<400> 8
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 Leu Leu Trp Thr Pro Leu Thr Gly Leu Lys Thr Leu His Leu Gly Ser
 20 25 30
 Cys Val Ile Thr Ala Asn Leu Gln Ala Ile Gln Lys Glu Phe Ser Glu
 35 40 45
 Ile Arg Asp Ser Val Ser Leu Asp Arg Cys Cys Phe Leu Arg His Leu
 50 55 60
 Val Arg Phe Tyr Leu Asp Arg Val Phe Lys Val Tyr Gln Thr Pro Asp
 65 70 75 80
 His His Thr Leu Arg Lys Ile Ser Ser Leu Ala Asn Ser Phe Leu Ile
 85 90 95
 Ile Lys Lys Asp Leu Ser Val Cys His Ser His Met Ala Cys His Cys
 100 105 110
 Gly Glu Glu Ala Met Glu Lys Tyr Asn Gln Ile Leu Ser His Phe Ile
 115 120 125
 Glu Leu Glu Leu Gln Ala Ala Val Val Lys Ala Leu Gly Glu Leu Gly
 130 135 140
 Ile Leu Leu Arg Trp Met Glu Glu Met Leu
 145 150

<210> 9
 <211> 130
 <212> PRT
 <213> Human

<400> 9
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 20 25 30

Arg Cys Cys Phe Leu Arg His Leu Val Arg Phe Tyr Leu Asp Arg Val
 35 40 45
 Phe Lys Val Tyr Gln Thr Pro Asp His His Thr Leu Arg Lys Ile Ser
 50 55 60
 Ser Leu Ala Asn Ser Phe Leu Ile Ile Lys Lys Asp Leu Ser Val Cys
 65 70 75 80
 His Ser His Met Ala Cys His Cys Gly Glu Glu Ala Met Glu Lys Tyr
 85 90 95
 Asn Gln Ile Leu Ser His Phe Ile Glu Leu Glu Leu Gln Ala Ala Val
 100 105 110
 Val Lys Ala Leu Gly Glu Leu Gly Ile Leu Leu Arg Trp Met Glu Glu
 115 120 125
 Met Leu
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<220>
 <221> CDS
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 Leu Thr Val Gly Ser Leu Ala Ala His Ala Pro Glu Asp Pro Ser Asp
 10 15 20

 ctg ctc cag cac gtg aaa ttc cag tcc agc aac ttt gaa aac atc ctg 150
 Leu Leu Gln His Val Lys Phe Gln Ser Ser Asn Phe Glu Asn Ile Leu
 25 30 35

 acg tgg gac agc ggg cca gag ggc acc cca gac acg gtc tac agc atc 198
 Thr Trp Asp Ser Gly Pro Glu Gly Thr Pro Asp Thr Val Tyr Ser Ile
 40 45 50 55

 gag tat aag acg tac gga gag agg gac tgg gtg gca aag aag ggc tgt 246
 Glu Tyr Lys Thr Tyr Gly Glu Arg Asp Trp Val Ala Lys Lys Gly Cys
 60 65 70

 cag cgg atc acc cgg aag tcc tgc aac ctg acg gtg gag acg ggc aac 294
 Gln Arg Ile Thr Arg Lys Ser Cys Asn Leu Thr Val Glu Thr Gly Asn
 75 80 85

 ctc acg gag ctc tac tat gcc agg gtc acc gct gtc agt gcg gga ggc 342
 Leu Thr Glu Leu Tyr Tyr Ala Arg Val Thr Ala Val Ser Ala Gly Gly
 90 95 100

 cgg tca gcc acc aag atg act gac agg ttc agc tct ctg cag cac act 390
 Arg Ser Ala Thr Lys Met Thr Asp Arg Phe Ser Ser Leu Gln His Thr
 105 110 115

 acc ctc aag cca cct gat gtg acc tgt atc tcc aaa gtg aga tcg att 438
 Thr Leu Lys Pro Asp Val Thr Cys Ile Ser Lys Val Arg Ser Ile
 120 125 130 135

 cag atg att gtt cat cct acc ccc acg cca atc cgt gca ggc gat ggc 486

Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro	Ile	Arg	Ala	Gly	Asp	Gly	
				140					145					150		
cac	cgg	cta	acc	ctg	gaa	gac	atc	ttc	cat	gac	ctg	ttc	tac	cac	tta	534
His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	His	Asp	Leu	Phe	Tyr	His	Leu	
			155				160					165				
gag	ctc	cag	gtc	aac	cgc	acc	tac	caa	atg	cac	ctt	gga	ggg	aag	cag	582
Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	Met	His	Leu	Gly	Gly	Lys	Gln	
		170				175						180				
aga	gaa	tat	gag	ttc	ttc	ggc	ctg	acc	cct	gac	aca	gag	ttc	ctt	ggc	630
Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr	Pro	Asp	Thr	Glu	Phe	Leu	Gly	
	185					190					195					
acc	atc	atg	att	tgc	gtt	ccc	acc	tgg	gcc	aag	gag	agt	gcc	ccc	tac	678
Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp	Ala	Lys	Glu	Ser	Ala	Pro	Tyr	
200				205					210					215		
atg	tgc	cga	gtg	aag	aca	ctg	cca	gac	cgg	aca	tgg	acc	tac	tcc	ttc	726
Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp	Arg	Thr	Trp	Thr	Tyr	Ser	Phe	
			220					225						230		
tcc	gga	gcc	ttc	ctg	ttc	tcc	atg	ggc	ttc	ctc	gtc	gca	gta	ctc	tgc	774
Ser	Gly	Ala	Phe	Leu	Phe	Ser	Met	Gly	Phe	Leu	Val	Ala	Val	Leu	Cys	
		235					240					245				
tac	ctg	agc	tac	aga	tat	gtc	acc	aag	ccg	cct	gca	cct	ccc	aac	tcc	822
Tyr	Leu	Ser	Tyr	Arg	Tyr	Val	Thr	Lys	Pro	Pro	Ala	Pro	Pro	Asn	Ser	
	250					255					260					
ctg	aac	gtc	cag	cga	gtc	ctg	act	ttc	cag	ccg	ctg	cgc	ttc	atc	cag	870
Leu	Asn	Val	Gln	Arg	Val	Leu	Thr	Phe	Gln	Pro	Leu	Arg	Phe	Ile	Gln	
	265					270					275					
gag	cac	gtc	ctg	atc	cct	gtc	ttt	gac	ctc	agc	ggc	ccc	agc	agt	ctg	918
Glu	His	Val	Leu	Ile	Pro	Val	Phe	Asp	Leu	Ser	Gly	Pro	Ser	Ser	Leu	
280				285					290						295	
gcc	cag	cct	gtc	cag	tac	tcc	cag	atc	agg	gtg	tct	gga	ccc	agg	gag	966
Ala	Gln	Pro	Val	Gln	Tyr	Ser	Gln	Ile	Arg	Val	Ser	Gly	Pro	Arg	Glu	
			300					305					310			
ccc	gca	gga	gct	cca	cag	cgg	cat	agc	ctg	tcc	gag	atc	acc	tac	tta	1014
Pro	Ala	Gly	Ala	Pro	Gln	Arg	His	Ser	Leu	Ser	Glu	Ile	Thr	Tyr	Leu	
		315					320					325				
ggg	cag	cca	gac	atc	tcc	atc	ctc	cag	ccc	tcc	aac	gtg	cca	cct	ccc	1062
Gly	Gln	Pro	Asp	Ile	Ser	Ile	Leu	Gln	Pro	Ser	Asn	Val	Pro	Pro	Pro	
	330					335						340				
cag	atc	ctc	tcc	cca	ctg	tcc	tat	gcc	cca	aac	gct	gcc	cct	gag	gtc	1110
Gln	Ile	Leu	Ser	Pro	Leu	Ser	Tyr	Ala	Pro	Asn	Ala	Ala	Pro	Glu	Val	
	345				350						355					
ggg	ccc	cca	tcc	tat	gca	cct	cag	gtg	acc	ccc	gaa	gct	caa	ttc	cca	1158
Gly	Pro	Pro	Ser	Tyr	Ala	Pro	Gln	Val	Thr	Pro	Glu	Ala	Gln	Phe	Pro	
360				365					370						375	
ttc	tac	gcc	cca	cag	gcc	atc	tct	aag	gtc	cag	cct	tcc	tcc	tat	gcc	1206
Phe	Tyr	Ala	Pro	Gln	Ala	Ile	Ser	Lys	Val	Gln	Pro	Ser	Ser	Tyr	Ala	
			380					385						390		

cct caa gcc act ccg gac agc tgg cct ccc tcc tat ggg gta tgc atg Pro Gln Ala Thr Pro Asp Ser Trp Pro Pro Ser Tyr Gly Val Cys Met 395 400 405	1254
gaa ggt tct ggc aaa gac tcc ccc act ggg aca ctt tct agt cct aaa Glu Gly Ser Gly Lys Asp Ser Pro Thr Gly Thr Leu Ser Ser Pro Lys 410 415 420	1302
cac ctt agg cct aaa ggt cag ctt cag aaa gag cca cca gct gga agc His Leu Arg Pro Lys Gly Gln Leu Gln Lys Glu Pro Pro Ala Gly Ser 425 430 435	1350
tgc atg tta ggt ggc ctt tct ctg cag gag gtg acc tcc ttg gct atg Cys Met Leu Gly Gly Leu Ser Leu Gln Glu Val Thr Ser Leu Ala Met 440 445 450 455	1398
gag gaa tcc caa gaa gca aaa tca ttg cac cag ccc ctg ggg att tgc Glu Glu Ser Gln Glu Ala Lys Ser Leu His Gln Pro Leu Gly Ile Cys 460 465 470	1446
aca gac aga aca tct gac cca aat gtg cta cac agt ggg gag gaa ggg Thr Asp Arg Thr Ser Asp Pro Asn Val Leu His Ser Gly Glu Glu Gly 475 480 485	1494
aca cca cag tac cta aag ggc cag ctc ccc ctc ctc tcc tca gtc cag Thr Pro Gln Tyr Leu Lys Gly Gln Leu Pro Leu Leu Ser Ser Val Gln 490 495 500	1542
atc gag ggc cac ccc atg tcc ctc cct ttg caa cct cct tcc ggt cca Ile Glu Gly His Pro Met Ser Leu Pro Leu Gln Pro Pro Ser Gly Pro 505 510 515	1590
tgt tcc ccc tcg gac caa ggt cca agt ccc tgg ggc ctg ctg gag tcc Cys Ser Pro Ser Asp Gln Gly Pro Ser Pro Trp Gly Leu Leu Glu Ser 520 525 530 535	1638
ctt gtg tgt ccc aag gat gaa gcc aag agc cca gcc cct gag acc tca Leu Val Cys Pro Lys Asp Glu Ala Lys Ser Pro Ala Pro Glu Thr Ser 540 545 550	1686
gac ctg gag cag ccc aca gaa ctg gat tct ctt ttc aga ggc ctg gcc Asp Leu Glu Gln Pro Thr Glu Leu Asp Ser Leu Phe Arg Gly Leu Ala 555 560 565	1734
ctg act gtg cag tgg gag tcc tgaggggaat gggaaaggct tgggtgcttcc Leu Thr Val Gln Trp Glu Ser 570	1785
tcctgtcccc tacccagtgt cacatccttg gctgtcaatc ccatgcctgc ccatgccaca cactctgcca tctggcctca gacgggtgcc cttgagagaa gcagagggag tggcatgcag ggcccttgcc atgggtgcgc tcctcaccgg aacaaagcag catgataagg actgcagcgg gggagctctg gggagcagct tgtgtagaca agcgcgtgct cgctgagccc tgcaaggcag aaatgacagt gcaaggagga aatgcagga aactcccag gtccagagcc ccacctccta acaccatgga ttcaaatgtgc tcagggaatt tgccctctct tgcctcattc ctggccagtt tcacaatcta gctcgacaga gcatgaggcc cctgcctctt ctgtcattgt tcaaaagggtg gaagagagcc tggaaaagaa ccaggcctgg aaaagaacca gaaggaggct gggcagaacc agaacaacct gcacttctgc caaggccagg gccagcagga cggcaggact ctaggagggg gtgtggcctg cagctcattc ccagccagg caactgcctg acgttgacag atttcagctt cattcctctg atagaacaaa gcgaaatgca ggtccaccag ggaggagagac acacaagcct tttctgcagg caggagtctc agaccctatc ctgagaatgg ggtttgaaag gaagggtgagg gctgtggccc ctggacgggt acaataacac actgtactga tgtcacaact ttgcaagctc	1845 1905 1965 2025 2085 2145 2205 2265 2325 2385 2445 2505 2565

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ataacaccta cctcatggag ttgtggtgaa gatgaaatga agtcatgtct ttaaagtgtc 2745
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aaaaaaaaaa atagcggccg cctcga 2831

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<211> 574
<212> PRT
<213> human

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Ala Pro Glu Asp Pro Ser Asp Leu Leu Gln His Val Lys Phe Gln Ser
20 25 30
Ser Asn Phe Glu Asn Ile Leu Thr Trp Asp Ser Gly Pro Glu Gly Thr
35 40 45
Pro Asp Thr Val Tyr Ser Ile Glu Tyr Lys Thr Tyr Gly Glu Arg Asp
50 55 60
Trp Val Ala Lys Lys Gly Cys Gln Arg Ile Thr Arg Lys Ser Cys Asn
65 70 75 80
Leu Thr Val Glu Thr Gly Asn Leu Thr Glu Leu Tyr Tyr Ala Arg Val
85 90 95
Thr Ala Val Ser Ala Gly Gly Arg Ser Ala Thr Lys Met Thr Asp Arg
100 105 110
Phe Ser Ser Leu Gln His Thr Thr Leu Lys Pro Pro Asp Val Thr Cys
115 120 125
Ile Ser Lys Val Arg Ser Ile Gln Met Ile Val His Pro Thr Pro Thr
130 135 140
Pro Ile Arg Ala Gly Asp Gly His Arg Leu Thr Leu Glu Asp Ile Phe
145 150 155 160
His Asp Leu Phe Tyr His Leu Glu Leu Gln Val Asn Arg Thr Tyr Gln
165 170 175
Met His Leu Gly Gly Lys Gln Arg Glu Tyr Glu Phe Phe Gly Leu Thr
180 185 190
Pro Asp Thr Glu Phe Leu Gly Thr Ile Met Ile Cys Val Pro Thr Trp
195 200 205
Ala Lys Glu Ser Ala Pro Tyr Met Cys Arg Val Lys Thr Leu Pro Asp
210 215 220
Arg Thr Trp Thr Tyr Ser Phe Ser Gly Ala Phe Leu Phe Ser Met Gly
225 230 235 240
Phe Leu Val Ala Val Leu Cys Tyr Leu Ser Tyr Arg Tyr Val Thr Lys
245 250 255
Pro Pro Ala Pro Pro Asn Ser Leu Asn Val Gln Arg Val Leu Thr Phe
260 265 270
Gln Pro Leu Arg Phe Ile Gln Glu His Val Leu Ile Pro Val Phe Asp
275 280 285
Leu Ser Gly Pro Ser Ser Leu Ala Gln Pro Val Gln Tyr Ser Gln Ile
290 295 300
Arg Val Ser Gly Pro Arg Glu Pro Ala Gly Ala Pro Gln Arg His Ser
305 310 315 320
Leu Ser Glu Ile Thr Tyr Leu Gly Gln Pro Asp Ile Ser Ile Leu Gln
325 330 335
Pro Ser Asn Val Pro Pro Pro Gln Ile Leu Ser Pro Leu Ser Tyr Ala
340 345 350
Pro Asn Ala Ala Pro Glu Val Gly Pro Pro Ser Tyr Ala Pro Gln Val
355 360 365
Thr Pro Glu Ala Gln Phe Pro Phe Tyr Ala Pro Gln Ala Ile Ser Lys
370 375 380
Val Gln Pro Ser Ser Tyr Ala Pro Gln Ala Thr Pro Asp Ser Trp Pro
385 390 395 400

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Pro	Ser	Tyr	Gly	Val	Cys	Met	Glu	Gly	Ser	Gly	Lys	Asp	Ser	Pro	Thr
				405					410					415	
Gly	Thr	Leu	Ser	Ser	Pro	Lys	His	Leu	Arg	Pro	Lys	Gly	Gln	Leu	Gln
			420					425					430		
Lys	Glu	Pro	Pro	Ala	Gly	Ser	Cys	Met	Leu	Gly	Gly	Leu	Ser	Leu	Gln
		435					440					445			
Glu	Val	Thr	Ser	Leu	Ala	Met	Glu	Glu	Ser	Gln	Glu	Ala	Lys	Ser	Leu
	450					455					460				
His	Gln	Pro	Leu	Gly	Ile	Cys	Thr	Asp	Arg	Thr	Ser	Asp	Pro	Asn	Val
465				470						475					480
Leu	His	Ser	Gly	Glu	Glu	Gly	Thr	Pro	Gln	Tyr	Leu	Lys	Gly	Gln	Leu
			485						490					495	
Pro	Leu	Leu	Ser	Ser	Val	Gln	Ile	Glu	Gly	His	Pro	Met	Ser	Leu	Pro
			500					505					510		
Leu	Gln	Pro	Pro	Ser	Gly	Pro	Cys	Ser	Pro	Ser	Asp	Gln	Gly	Pro	Ser
		515					520					525			
Pro	Trp	Gly	Leu	Leu	Glu	Ser	Leu	Val	Cys	Pro	Lys	Asp	Glu	Ala	Lys
	530					535					540				
Ser	Pro	Ala	Pro	Glu	Thr	Ser	Asp	Leu	Glu	Gln	Pro	Thr	Glu	Leu	Asp
545				550						555					560
Ser	Leu	Phe	Arg	Gly	Leu	Ala	Leu	Thr	Val	Gln	Trp	Glu	Ser		
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<210>	12
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<212>	PRT
<213>	human

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<210> 13
<211> 211

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<212> PRT
<213> human

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Asn Phe Glu Asn Ile Leu Thr Trp Asp Ser Gly Pro Glu Gly Thr Pro
20 25 30
Asp Thr Val Tyr Ser Ile Glu Tyr Lys Thr Tyr Gly Glu Arg Asp Trp
35 40 45
Val Ala Lys Lys Gly Cys Gln Arg Ile Thr Arg Lys Ser Cys Asn Leu
50 55 60
Thr Val Glu Thr Gly Asn Leu Thr Glu Leu Tyr Tyr Ala Arg Val Thr
65 70 75 80
Ala Val Ser Ala Gly Gly Arg Ser Ala Thr Lys Met Thr Asp Arg Phe
85 90 95
Ser Ser Leu Gln His Thr Thr Leu Lys Pro Pro Asp Val Thr Cys Ile
100 105 110
Ser Lys Val Arg Ser Ile Gln Met Ile Val His Pro Thr Pro Thr Pro
115 120 125
Ile Arg Ala Gly Asp Gly His Arg Leu Thr Leu Glu Asp Ile Phe His
130 135 140
Asp Leu Phe Tyr His Leu Glu Leu Gln Val Asn Arg Thr Tyr Gln Met
145 150 155 160
His Leu Gly Gly Lys Gln Arg Glu Tyr Glu Phe Phe Gly Leu Thr Pro
165 170 175
Asp Thr Glu Phe Leu Gly Thr Ile Met Ile Cys Val Pro Thr Trp Ala
180 185 190
Lys Glu Ser Ala Pro Tyr Met Cys Arg Val Lys Thr Leu Pro Asp Arg
195 200 205
Thr Trp Thr
210

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<212> DNA
<213> Human

<220>
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tgg aca agt ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg 98
Trp Thr Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu
15 20 25
ctc aca gat gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta 146
Leu Thr Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val
30 35 40
ctc tca acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg 194
Leu Ser Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala
45 50 55
cct gga gaa aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag 242
Pro Gly Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu
60 65 70 75

agc ctg tac acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc Ser Leu Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu 80 85 90	290
act gaa ggt cct gag tgt gat gtc act gat gac atc acg gcc act gtg Thr Glu Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val 95 100 105	338
cca tac aac ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc Pro Tyr Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala 110 115 120	386
tgg agc atc ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc Trp Ser Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr 125 130 135	434
cga cct ggg atg gag atc acc aaa gat ggc ttc cac ctg gtt att gag Arg Pro Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu 140 145 150 155	482
ctg gag gac ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg agg Leu Glu Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg 160 165 170	530
agg gag cct ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt Arg Glu Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly 175 180 185	578
att cca gtg cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg Ile Pro Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val 190 195 200	626
aag gcc cag aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc Lys Ala Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser 205 210 215	674
cag aca gaa tgt gtg gag gtg caa gga gag gcc att ccc ctg gta ctg Gln Thr Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu 220 225 230 235	722
gcc ctg ttt gcc ttt gtt ggc ttc atg ctg atc ctt gtg gtc gtg cca Ala Leu Phe Ala Phe Val Gly Phe Met Leu Ile Leu Val Val Val Pro 240 245 250	770
ctg ttc gtc tgg aaa atg ggc cgg ctg ctc cag tac tcc tgt tgc ccc Leu Phe Val Trp Lys Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro 255 260 265	818
gtg gtg gtc ctc cca gac acc ttg aaa ata acc aat tca ccc cag aag Val Val Val Leu Pro Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Lys 270 275 280	866
tta atc agc tgc aga agg gag gag gtg gat gcc tgt gcc acg gct gtg Leu Ile Ser Cys Arg Arg Glu Glu Val Asp Ala Cys Ala Thr Ala Val 285 290 295	914
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 <212> PRT
 <213> Human

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 Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
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 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80
 His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
 85 90 95
 Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
 100 105 110
 Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
 115 120 125
 His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
 130 135 140
 Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
 145 150 155 160
 Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
 165 170 175
 Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
 180 185 190
 Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
 195 200 205
 Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
 210 215 220
 Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu Phe Ala Phe
 225 230 235 240
 Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe Val Trp Lys
 245 250 255
 Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val Val Leu Pro
 260 265 270
 Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Lys Leu Ile Ser Cys Arg
 275 280 285
 Arg Glu Glu Val Asp Ala Cys Ala Thr Ala Val Met Ser Pro Glu Glu
 290 295 300
 Leu Leu Arg Ala Trp Ile Ser
 305 310

<210> 16
 <211> 203
 <212> PRT
 <213> human

<400> 16
 Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1 5 10 15
 Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
 20 25 30
 Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
 35 40 45
 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60

13

Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
 65 70 75 80
 Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro
 195 200

<210> 17
 <211> 201
 <212> PRT
 <213> Homo sapiens

<400> 17
 Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1 5 10 15
 Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
 20 25 30
 Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
 35 40 45
 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60
 Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
 65 70 75 80
 Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala
 195 200

<210> 18
 <211> 201
 <212> PRT
 <213> Homo sapiens

<400> 18
 Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1 5 10 15
 Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
 20 25 30

14

Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
 35 40 45
 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60
 Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
 65 70 75 80
 Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala
 195 200

<210> 19
 <211> 196
 <212> PRT
 <213> Homo sapiens

<400> 19
 Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met Lys His
 1 5 10 15
 Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val Tyr Tyr
 20 25 30
 Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser His Ile
 35 40 45
 Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu Cys Asp
 50 55 60
 Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg Val Arg
 65 70 75 80
 Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys His Pro
 85 90 95
 Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu Ile Thr
 100 105 110
 Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly Pro Gln
 115 120 125
 Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala Glu Glu
 130 135 140
 His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu Glu Thr
 145 150 155 160
 Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe Val Lys
 165 170 175
 Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val Glu Val
 180 185 190
 Gln Gly Glu Ala
 195

<210> 20
 <211> 203
 <212> PRT
 <213> Homo sapiens

<400> 20

15

Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1 5 10 15
 Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
 20 25 30
 Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
 35 40 45
 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60
 Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
 65 70 75 80
 Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro
 195 200

<210> 21
 <211> 196
 <212> PRT
 <213> Homo sapiens

<400> 21
 Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met Lys His
 1 5 10 15
 Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val Tyr Tyr
 20 25 30
 Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser His Ile
 35 40 45
 Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu Cys Asp
 50 55 60
 Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg Val Arg
 65 70 75 80
 Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys His Pro
 85 90 95
 Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu Ile Pro
 100 105 110
 Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly Pro Gln
 115 120 125
 Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala Glu Glu
 130 135 140
 His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu Glu Thr
 145 150 155 160
 Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe Val Lys
 165 170 175
 Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val Glu Val
 180 185 190
 Gln Gly Glu Ala
 195

<210> 22
 <211> 1382

<212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> (132)...(1034)

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<400> 22
tcgacccacg cgctccgcgt gcgactcaga cctcagctcc aacatatgca ttctgaagaa      60
agatggctga gatggacaga atgctttatt ttggaaagaa acaatgttct aggtcaaact      120
gagtctacca a atg cag act ttc aca atg gtt cta gaa gaa atc tgg aca      170
          Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr
          1              5              10

agt ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca      218
Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr
          15              20              25

gat gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca      266
Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
          30              35              40              45

acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga      314
Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
          50              55              60

gaa aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg      362
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
          65              70              75

tac acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa      410
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
          80              85              90

ggg cct gag tgt gat gtc act gat gac atc acg gcc act gtg cca tac      458
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
          95              100              105

aac ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc      506
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
          110              115              120              125

atc ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc cga cct      554
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
          130              135              140

ggg atg gag atc ccc aaa cat ggc ttc cac ctg gtt att gag ctg gag      602
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
          145              150              155

gac ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg acg agg gag      650
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
          160              165              170

cct ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca      698
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
          175              180              185

gtg cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc      746
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
          190              195              200              205

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cag aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca 794
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 210 215 220

gaa tgt gtg gag gtg caa gga gag gcc att ccc ctg gta ctg gcc ctg 842
 Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu
 225 230 235

ttt gcc ttt gtt ggc ttc atg ctg atc ctt gtg gtc gtg cca ctg ttc 890
 Phe Ala Phe Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe
 240 245 250

gtc tgg aaa atg ggc cgg ctg ctc cag tac tcc tgt tgc ccc gtg gtg 938
 Val Trp Lys Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val
 255 260 265

gtc ctc cca gac acc ttg aaa ata acc aat tca ccc cag gtt aat cag 986
 Val Leu Pro Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Val Asn Gln
 270 275 280 285

ctg cag aag gga gga ggt gga tgc ctg tgc cac ggc tgt gat gtc tcc 1034
 Leu Gln Lys Gly Gly Gly Cys Leu Cys His Gly Cys Asp Val Ser
 290 295 300

tgaggaactc ctcagggcct ggatctcata tcaggtttgc ggaagggccc aggtgaagcc 1094
 gagaacctgg tctgcatgac atggaaacca tgaggggaca agttgtgtt ctgttttccg 1154
 ccacggacaa gggatgagag aagtaggaag agcctgttgt ctacaagtct agaagcaacc 1214
 atcagaggca ggggtggtttg tctaacagaa caactgactg aggctatggg ggttgtgacc 1274
 tctagacttt gggcttccac ttgcttggt gagcaaccct gggaaaagtg acttcatccc 1334
 ttcggtccca agttttctca tctgtaatgg gggatcccta caaaactg 1382

<210> 23
 <211> 301
 <212> PRT
 <213> Homo sapiens

<400> 23
 Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
 1 5 10 15
 Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
 20 25 30
 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80
 His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
 85 90 95
 Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
 100 105 110
 Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
 115 120 125
 His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
 130 135 140
 Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
 145 150 155 160
 Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala
 165 170 175
 Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
 180 185 190
 Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe


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<210> 24
<211> 1764
<212> DNA
<213> Homo sapiens
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<220>
<221> CDS
<222> (34) ... (1752)
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<400> 24																	
tagaggccaa	gggagggctc	tgtgccagcc	ccg	atg	agg	acg	ctg	ctg	acc	atc							54
				Met	Arg	Thr	Leu	Leu	Thr	Ile							
				1					5								
ttg	act	gtg	gga	tcc	ctg	gct	gct	cac	gcc	cct	gag	gac	ccc	tcg	gat		102
Leu	Thr	Val	Gly	Ser	Leu	Ala	Ala	His	Ala	Pro	Glu	Asp	Pro	Ser	Asp		
		10					15					20					
ctg	ctc	cag	cac	gtg	aaa	ttc	cag	tcc	agc	aac	ttt	gaa	aac	atc	ctg		150
Leu	Leu	Gln	His	Val	Lys	Phe	Gln	Ser	Ser	Asn	Phe	Glu	Asn	Ile	Leu		
		25				30					35						
acg	tgg	gac	agc	ggg	cca	gag	ggc	acc	cca	gac	acg	gtc	tac	agc	atc		198
Thr	Trp	Asp	Ser	Gly	Pro	Glu	Gly	Thr	Pro	Asp	Thr	Val	Tyr	Ser	Ile		
		40			45					50					55		
gag	tat	aag	acg	tac	gga	gag	agg	gac	tgg	gtg	gca	aag	aag	ggc	tgt		246
Glu	Tyr	Lys	Thr	Tyr	Gly	Glu	Arg	Asp	Trp	Val	Ala	Lys	Lys	Gly	Cys		
				60					65					70			
cag	cgg	atc	acc	cgg	aag	tcc	tgc	aac	ctg	acg	gtg	gag	acg	ggc	aac		294
Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn	Leu	Thr	Val	Glu	Thr	Gly	Asn		
			75					80					85				
ctc	acg	gag	ctc	tac	tat	gcc	agg	gtc	acc	gct	gtc	agt	gcg	gga	ggc		342
Leu	Thr	Glu	Leu	Tyr	Tyr	Ala	Arg	Val	Thr	Ala	Val	Ser	Ala	Gly	Gly		
		90					95					100					
cgg	tca	gcc	acc	aag	atg	act	gac	agg	ttc	agc	tct	ctg	cag	cac	act		390
Arg	Ser	Ala	Thr	Lys	Met	Thr	Asp	Arg	Phe	Ser	Ser	Leu	Gln	His	Thr		
		105				110					115						
acc	ctc	aag	cca	cct	gat	gtg	acc	tgt	atc	tcc	aaa	gtg	aga	tcg	att		438
Thr	Leu	Lys	Pro	Pro	Asp	Val	Thr	Cys	Ile	Ser	Lys	Val	Arg	Ser	Ile		
		120			125					130					135		
cag	atg	att	gtt	cat	cct	acc	ccc	acg	cca	atc	cgt	gca	ggc	gat	ggc		486
Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro	Ile	Arg	Ala	Gly	Asp	Gly		

19

140	145	150	
cac cgg cta acc ctg gaa gac atc ttc cat gac ctg ttc tac cac tta His Arg Leu Thr Leu Glu Asp Ile Phe His Asp Leu Phe Tyr His Leu 155 160 165			534
gag ctc cag gtc aac cgc acc tac caa atg cac ctt gga ggg aag cag Glu Leu Gln Val Asn Arg Thr Tyr Gln Met His Leu Gly Gly Lys Gln 170 175 180			582
aga gaa tat gag ttc ttc ggc ctg acc cct gac aca gag ttc ctt ggc Arg Glu Tyr Glu Phe Phe Gly Leu Thr Pro Asp Thr Glu Phe Leu Gly 185 190 195			630
acc atc atg att tgc gtt ccc acc tgg gcc aag gag agt gcc ccc tac Thr Ile Met Ile Cys Val Pro Thr Trp Ala Lys Glu Ser Ala Pro Tyr 200 205 210 215			678
atg tgc cga gtg aag aca ctg cca gac cgg aca tgg acc ggt gga ggc Met Cys Arg Val Lys Thr Leu Pro Asp Arg Thr Trp Thr Gly Gly Gly 220 225 230			726
ggt tca ggc gga ggt ggc tct ggc ggt ggc gga tgc gcc tcc acc aag Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Thr Lys 235 240 245			774
ggc cca tgc gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggg Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly 250 255 260			822
ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro 265 270 275			870
gtg acg gtg tgc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr 280 285 290 295			918
ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc agc agc gtg Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val 300 305 310			966
gtg acc gtg ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn 315 320 325			1014
gtg aat cac aag ccc agc aac acc aag gtg gac aag aaa gtt gag ccc Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro 330 335 340			1062
aaa tct tgt gac aaa act cac aca tgc cca ccg tgc cca gca cct gaa Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu 345 350 355			1110
gcc gag ggg gca ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp 360 365 370 375			1158
acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp 380 385 390			1206

20

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gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc      1254
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
              395                      400                      405

gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac      1302
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
              410                      415                      420

agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg      1350
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
              425                      430                      435

ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca      1398
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
              440                      445                      450                      455

tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa      1446
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
              460                      465                      470

cca cag gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac      1494
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
              475                      480                      485

cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc      1542
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
              490                      495                      500

gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc      1590
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
              505                      510                      515

acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag      1638
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
              520                      525                      530                      535

ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc      1686
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
              540                      545                      550

tcc gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc      1734
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
              555                      560                      565

tcc ctg tct ccg ggt aaa taatctagat ct      1764
Ser Leu Ser Pro Gly Lys
              570

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<210> 25
<211> 573
<212> PRT
<213> Homo sapiens

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<400> 25
Met Arg Thr Leu Leu Thr Ile Leu Thr Val Gly Ser Leu Ala Ala His
 1          5          10          15
Ala Pro Glu Asp Pro Ser Asp Leu Leu Gln His Val Lys Phe Gln Ser
 20          25          30
Ser Asn Phe Glu Asn Ile Leu Thr Trp Asp Ser Gly Pro Glu Gly Thr
 35          40          45
Pro Asp Thr Val Tyr Ser Ile Glu Tyr Lys Thr Tyr Gly Glu Arg Asp

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50	55	60
Trp Val Ala Lys Lys Gly Cys Gln Arg Ile Thr Arg Lys Ser Cys Asn		
65	70	75
Leu Thr Val Glu Thr Gly Asn Leu Thr Glu Leu Tyr Tyr Ala Arg Val		
	85	90
Thr Ala Val Ser Ala Gly Gly Arg Ser Ala Thr Lys Met Thr Asp Arg		95
	100	105
Phe Ser Ser Leu Gln His Thr Thr Leu Lys Pro Pro Asp Val Thr Cys		110
	115	120
Ile Ser Lys Val Arg Ser Ile Gln Met Ile Val His Pro Thr Pro Thr		125
	130	135
Pro Ile Arg Ala Gly Asp Gly His Arg Leu Thr Leu Glu Asp Ile Phe		140
145	150	155
His Asp Leu Phe Tyr His Leu Glu Leu Gln Val Asn Arg Thr Tyr Gln		160
	165	170
Met His Leu Gly Gly Lys Gln Arg Glu Tyr Glu Phe Phe Gly Leu Thr		175
	180	185
Pro Asp Thr Glu Phe Leu Gly Thr Ile Met Ile Cys Val Pro Thr Trp		190
	195	200
Ala Lys Glu Ser Ala Pro Tyr Met Cys Arg Val Lys Thr Leu Pro Asp		205
	210	215
Arg Thr Trp Thr Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly		220
225	230	235
Gly Gly Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro		240
	245	250
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val		255
	260	265
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala		270
	275	280
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly		285
	290	295
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly		300
305	310	315
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys		320
	325	330
Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys		335
	340	345
Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu		350
	355	360
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu		365
	370	375
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys		380
385	390	395
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys		400
	405	410
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu		415
	420	425
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys		430
	435	440
Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys		445
	450	455
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser		460
465	470	475
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys		480
	485	490
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln		495
	500	505
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly		510
	515	520
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln		525
	530	535
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn		540

545	550										555				560	
His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys				
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				<210>	26											
				<211>	556											
				<212>	PRT											
				<213>	Homo sapiens											
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1				5					10					15		
Asn	Phe	Glu	Asn	Ile	Leu	Thr	Trp	Asp	Ser	Gly	Pro	Glu	Gly	Thr	Pro	
			20					25					30			
Asp	Thr	Val	Tyr	Ser	Ile	Glu	Tyr	Lys	Thr	Tyr	Gly	Glu	Arg	Asp	Trp	
		35					40					45				
Val	Ala	Lys	Lys	Gly	Cys	Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn	Leu	
	50					55					60					
Thr	Val	Glu	Thr	Gly	Asn	Leu	Thr	Glu	Leu	Tyr	Tyr	Ala	Arg	Val	Thr	
65					70					75					80	
Ala	Val	Ser	Ala	Gly	Gly	Arg	Ser	Ala	Thr	Lys	Met	Thr	Asp	Arg	Phe	
				85					90					95		
Ser	Ser	Leu	Gln	His	Thr	Thr	Leu	Lys	Pro	Pro	Asp	Val	Thr	Cys	Ile	
			100					105					110			
Ser	Lys	Val	Arg	Ser	Ile	Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro	
		115					120					125				
Ile	Arg	Ala	Gly	Asp	Gly	His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	His	
		130				135					140					
Asp	Leu	Phe	Tyr	His	Leu	Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	Met	
145					150					155					160	
His	Leu	Gly	Gly	Lys	Gln	Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr	Pro	
				165					170					175		
Asp	Thr	Glu	Phe	Leu	Gly	Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp	Ala	
			180					185						190		
Lys	Glu	Ser	Ala	Pro	Tyr	Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp	Arg	
		195					200					205				
Thr	Trp	Thr	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	
	210				215							220				
Gly	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	
225					230					235					240	
Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	
				245					250					255		
Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	
			260					265						270		
Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	
		275					280					285				
Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	
		290				295						300				
Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	
305					310											

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 420 425 430
 Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
 435 440 445
 Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 450 455 460
 Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 465 470 475 480
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 485 490 495
 Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 500 505 510
 Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 515 520 525
 Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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 Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 545 550 555

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 ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca gat 98
 Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp
 15 20 25 30
 gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca acc 146
 Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr
 35 40 45
 aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga gaa 194
 Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu
 50 55 60
 aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg tac 242
 Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr
 65 70 75
 acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa ggt 290
 Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly
 80 85 90
 cct gag tgt gat gtc act gat gac atc acg gcc act gtg cca tac aac 338
 Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn
 95 100 105 110
 ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc atc 386
 Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile
 115 120 125
 ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc cga cct ggg 434

Leu	Lys	His	Pro	Phe	Asn	Arg	Asn	Ser	Thr	Ile	Leu	Thr	Arg	Pro	Gly		
			130					135					140				
atg	gag	atc	ccc	aaa	cat	ggc	ttc	cac	ctg	gtt	att	gag	ctg	gag	gac	482	
Met	Glu	Ile	Pro	Lys	His	Gly	Phe	His	Leu	Val	Ile	Glu	Leu	Glu	Asp		
			145				150					155					
ctg	ggg	ccc	cag	ttt	gag	ttc	ctt	gtg	gcc	tac	tgg	acg	agg	gag	cct	530	
Leu	Gly	Pro	Gln	Phe	Glu	Phe	Leu	Val	Ala	Tyr	Trp	Thr	Arg	Glu	Pro		
			160				165				170						
ggg	gcc	gag	gaa	cat	gtc	aaa	atg	gtg	agg	agt	ggg	ggg	att	cca	gtg	578	
Gly	Ala	Glu	Glu	His	Val	Lys	Met	Val	Arg	Ser	Gly	Gly	Ile	Pro	Val		
					180					185					190		
cac	cta	gaa	acc	atg	gag	cca	ggg	gct	gca	tac	tgt	gtg	aag	gcc	cag	626	
His	Leu	Glu	Thr	Met	Glu	Pro	Gly	Ala	Ala	Tyr	Cys	Val	Lys	Ala	Gln		
				195					200					205			
aca	ttc	gtg	aag	gcc	att	ggg	agg	tac	agc	gcc	ttc	agc	cag	aca	gaa	674	
Thr	Phe	Val	Lys	Ala	Ile	Gly	Arg	Tyr	Ser	Ala	Phe	Ser	Gln	Thr	Glu		
				210				215					220				
tgt	gtg	gag	gtg	caa	gga	gag	gcc	gga	ggg	ggg	ggc	agt	gga	ggc	ggc	722	
Cys	Val	Glu	Val	Gln	Gly	Glu	Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly		
			225				230					235					
ggg	agc	gga	ggc	ggg	ggc	agt	cga	act	gtg	gct	gca	cca	tct	gtc	ttc	770	
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe		
			240			245					250						
atc	ttc	ccg	cca	tct	gat	gag	cag	ttg	aaa	tct	gga	act	gcc	tct	gtt	818	
Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val		
					260					265					270		
gtg	tgc	ctg	ctg	aat	aac	ttc	tat	ccc	aga	gag	gcc	aaa	gta	cag	tgg	866	
Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp		
				275				280						285			
aag	gtg	gat	aac	gcc	ctc	caa	tcg	ggg	aac	tcc	cag	gag	agt	gtc	aca	914	
Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr		
			290					295					300				
gag	cag	gac	agc	aag	gac	agc	acc	tac	agc	ctc	agc	agc	acc	ctg	acg	962	
Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr		
			305				310					315					
ctg	agc	aaa	gca	gac	tac	gag	aaa	cac	aaa	gtc	tac	gcc	tgc	gaa	gtc	1010	
Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val		
			320			325					330						
acc	cat	cag	ggc	ctg	agc	tcg	ccc	gtc	aca	aag	agc	ttc	aac	agg	gga	1058	
Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly		
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gag	tgt	taa	tctagaggcg	cgcc												1081	
Glu	Cys	*															

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<211> 352

25

<212> PRT

<213> Homo sapiens

<400> 28

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Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
           20           25           30
Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
           35           40           45
Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
           50           55           60
Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
65           70           75           80
His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
           85           90           95
Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
           100          105          110
Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
           115          120          125
His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
130          135          140
Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
145          150          155          160
Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala
           165          170          175
Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
           180          185          190
Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
           195          200          205
Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
210          215          220
Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
225          230          235          240
Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
           245          250          255
Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
           260          265          270
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
           275          280          285
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
290          295          300
Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
305          310          315          320
Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
           325          330          335
Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
           340          345          350

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<211> 323

<212> PRT

<213> Homo sapiens

<400> 29

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Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
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Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
           20           25           30
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
           35           40           45
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu

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50	55	60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr		
65	70	75
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser		80
	85	90
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro		95
	100	105
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu		110
	115	120
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu		125
	130	135
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro		140
145	150	155
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala		160
	165	170
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr		175
	180	185
Glu Cys Val Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly		190
	195	200
Gly Gly Ser Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val		205
	210	215
Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser		220
225	230	235
Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln		240
	245	250
Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val		255
	260	265
Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu		270
	275	280
Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu		285
	290	295
Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg		300
305	310	315
Gly Glu Cys		320

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<220>
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1 5	
ttg act gtg gga tcc ctg gct gct cac gcc cct gag gac ccc tcg gat	102
Leu Thr Val Gly Ser Leu Ala Ala His Ala Pro Glu Asp Pro Ser Asp	
10 15 20	
ctg ctc cag cac gtg aaa ttc cag tcc agc aac ttt gaa aac atc ctg	150
Leu Leu Gln His Val Lys Phe Gln Ser Ser Asn Phe Glu Asn Ile Leu	
25 30 35	
acg tgg gac agc ggg cca gag ggc acc cca gac acg gtc tac agc atc	198
Thr Trp Asp Ser Gly Pro Glu Gly Thr Pro Asp Thr Val Tyr Ser Ile	
40 45 50 55	

gag tat aag acg tac gga gag agg gac tgg gtg gca aag aag ggc tgt Glu Tyr Lys Thr Tyr Gly Glu Arg Asp Trp Val Ala Lys Lys Gly Cys 60 65 70	246
cag cgg atc acc cgg aag tcc tgc aac ctg acg gtg gag acg ggc aac Gln Arg Ile Thr Arg Lys Ser Cys Asn Leu Thr Val Glu Thr Gly Asn 75 80 85	294
ctc acg gag ctc tac tat gcc agg gtc acc gct gtc agt gcg gga ggc Leu Thr Glu Leu Tyr Tyr Ala Arg Val Thr Ala Val Ser Ala Gly Gly 90 95 100	342
cgg tca gcc acc aag atg act gac agg ttc agc tct ctg cag cac act Arg Ser Ala Thr Lys Met Thr Asp Arg Phe Ser Ser Leu Gln His Thr 105 110 115	390
acc ctc aag cca cct gat gtg acc tgt atc tcc aaa gtg aga tcg att Thr Leu Lys Pro Pro Asp Val Thr Cys Ile Ser Lys Val Arg Ser Ile 120 125 130 135	438
cag atg att gtt cat cct acc ccc acg cca atc cgt gca ggc gat ggc Gln Met Ile Val His Pro Thr Pro Thr Ile Arg Ala Gly Asp Gly 140 145 150	486
cac cgg cta acc ctg gaa gac atc ttc cat gac ctg ttc tac cac tta His Arg Leu Thr Leu Glu Asp Ile Phe His Asp Leu Phe Tyr His Leu 155 160 165	534
gag ctc cag gtc aac cgc acc tac caa atg cac ctt gga ggg aag cag Glu Leu Gln Val Asn Arg Thr Tyr Gln Met His Leu Gly Gly Lys Gln 170 175 180	582
aga gaa tat gag ttc ttc ggc ctg acc cct gac aca gag ttc ctt ggc Arg Glu Tyr Glu Phe Phe Gly Leu Thr Pro Asp Thr Glu Phe Leu Gly 185 190 195	630
acc atc atg att tgc gtt ccc acc tgg gcc aag gag agt gcc ccc tac Thr Ile Met Ile Cys Val Pro Thr Trp Ala Lys Glu Ser Ala Pro Tyr 200 205 210 215	678
atg tgc cga gtg aag aca ctg cca gac cgg aca tgg acc gct agc acc Met Cys Arg Val Lys Thr Leu Pro Asp Arg Thr Trp Thr Ala Ser Thr 220 225 230	726
aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser 235 240 245	774
ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu 250 255 260	822
ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc ggc gtg cac Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His 265 270 275	870
acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc agc agc Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser 280 285 290 295	918
gtg gtg acc gtg ccc tcc agc agc ttg ggc acc cag acc tac atc tgc Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys	966

300	305	310	
aac gtg aat cac aag ccc agc aac acc aag gtg gac aag aaa gtt gag Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu 315 320 325			1014
ccc aaa tct tgt gac aaa act cac aca tgc cca ccg tgc cca gca cct Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro 330 335 340			1062
gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys 345 350 355			1110
gac acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val 360 365 370 375			1158
gac gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp 380 385 390			1206
ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 395 400 405			1254
aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp 410 415 420			1302
tgg ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu 425 430 435			1350
cca gcc ccc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg 440 445 450 455			1398
gaa cca cag gtg tac acc ctg ccc cca tcc ccg gat gag ctg acc aag Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys 460 465 470			1446
aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp 475 480 485			1494
atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys 490 495 500			1542
acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser 505 510 515			1590
aag ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser 520 525 530 535			1638
tgc tcc gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser 540 545 550			1686

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 Leu Ser Leu Ser Pro Gly Lys
 555

1714

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 <212> PRT
 <213> Homo sapiens

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 Ser Asn Phe Glu Asn Ile Leu Thr Trp Asp Ser Gly Pro Glu Gly Thr
 35 40 45
 Pro Asp Thr Val Tyr Ser Ile Glu Tyr Lys Thr Tyr Gly Glu Arg Asp
 50 55 60
 Trp Val Ala Lys Lys Gly Cys Gln Arg Ile Thr Arg Lys Ser Cys Asn
 65 70 75 80
 Leu Thr Val Glu Thr Gly Asn Leu Thr Glu Leu Tyr Tyr Ala Arg Val
 85 90 95
 Thr Ala Val Ser Ala Gly Gly Arg Ser Ala Thr Lys Met Thr Asp Arg
 100 105 110
 Phe Ser Ser Leu Gln His Thr Thr Leu Lys Pro Pro Asp Val Thr Cys
 115 120 125
 Ile Ser Lys Val Arg Ser Ile Gln Met Ile Val His Pro Thr Pro Thr
 130 135 140
 Pro Ile Arg Ala Gly Asp Gly His Arg Leu Thr Leu Glu Asp Ile Phe
 145 150 155 160
 His Asp Leu Phe Tyr His Leu Glu Leu Gln Val Asn Arg Thr Tyr Gln
 165 170 175
 Met His Leu Gly Gly Lys Gln Arg Glu Tyr Glu Phe Phe Gly Leu Thr
 180 185 190
 Pro Asp Thr Glu Phe Leu Gly Thr Thr Ile Met Ile Cys Val Pro Thr Trp
 195 200 205
 Ala Lys Glu Ser Ala Pro Tyr Met Cys Arg Val Lys Thr Leu Pro Asp
 210 215 220
 Arg Thr Trp Thr Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 225 230 235 240
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 245 250 255
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 260 265 270
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 275 280 285
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 290 295 300
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 305 310 315 320
 Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 325 330 335
 Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 340 345 350
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 355 360 365
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 370 375 380
 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 385 390 395 400
 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

Leu	Thr	Val	405	Leu	His	Gln	Asp	Trp	410	Leu	Asn	Gly	Lys	Glu	Tyr	415	Lys	Cys
			420	Asn	Lys	Ala	Leu	Pro	425	Ala	Pro	Ile	Glu	Lys	Thr	430	Ile	Ser
Lys	Val	Ser	435	Gly	Gln	Pro	Arg	Glu	440	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
			450	Asp	Glu	Leu	Thr	Lys	455	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val
Ser	Arg	Asp	465	Tyr	Pro	Ser	Asp	Ile	470	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	
Lys	Gly	Phe	485	Asn	Tyr	Lys	Thr	Thr	490	Pro	Pro	Val	Leu	Asp	Ser	Asp		
Gln	Pro	Glu	500	Asn	Tyr	Lys	Thr	Thr	505	Pro	Pro	Val	Leu	Asp	Ser	Asp		
Gly	Ser	Phe	515	Asn	Val	Phe	Ser	Cys	520	Ser	Val	Met	His	Glu	Ala	Leu	His	
Gln	Gln	Gly	530	Asn	Val	Phe	Ser	Cys	535	Ser	Val	Met	His	Glu	Ala	Leu	His	
Asn	His	Tyr	545	Thr	Gln	Lys	Ser	Leu	550	Ser	Leu	Ser	Pro	Gly	Lys			

<210> 32

<211> 541

<212> PRT

<213> Homo sapiens

<400> 32

Pro	Glu	Asp	Pro	Ser	Asp	Leu	Leu	Gln	His	Val	Lys	Phe	Gln	Ser	Ser			
1				5					10					15				
Asn	Phe	Glu	Asn	Ile	Leu	Thr	Trp	Asp	Ser	Gly	Pro	Glu	Gly	Thr	Pro			
			20					25					30					
Asp	Thr	Val	Tyr	Ser	Ile	Glu	Tyr	Lys	Thr	Tyr	Gly	Glu	Arg	Asp	Trp			
			35					40					45					
Val	Ala	Lys	Lys	Gly	Cys	Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn	Leu			
			50					55				60						
Thr	Val	Glu	Thr	Gly	Asn	Leu	Thr	Glu	Leu	Tyr	Ala	Arg	Val	Thr				
65					70					75				80				
Ala	Val	Ser	Ala	Gly	Gly	Arg	Ser	Ala	Thr	Lys	Met	Thr	Asp	Arg	Phe			
			85					90					95					
Ser	Ser	Leu	Gln	His	Thr	Thr	Leu	Lys	Pro	Pro	Asp	Val	Thr	Cys	Ile			
			100					105					110					
Ser	Lys	Val	Arg	Ser	Ile	Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro			
			115					120					125					
Ile	Arg	Ala	Gly	Asp	Gly	His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	His			
			130					135				140						
Asp	Leu	Phe	Tyr	His	Leu	Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	Met			
145					150					155				160				
His	Leu	Gly	Gly	Lys	Gln	Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr	Pro			
			165					170					175					
Asp	Thr	Glu	Phe	Leu	Gly	Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp	Ala			
			180					185					190					
Lys	Glu	Ser	Ala	Pro	Tyr	Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp	Arg			
			195					200					205					
Thr	Trp	Thr	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro			
			210					215					220					
Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val			
225					230					235				240				
Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala			
			245							250				255				
Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly			
			260					265					270					
Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly			
			275					280					285					

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 290 295 300
 Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
 305 310 315 320
 Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 325 330 335
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 340 345 350
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 355 360 365
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 370 375 380
 Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 385 390 395 400
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 405 410 415
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 420 425 430
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 435 440 445
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 450 455 460
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 465 470 475 480
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 485 490 495
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 500 505 510
 Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 515 520 525
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 530 535 540

<210> 33
 <211> 1011
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
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<400> 33
 atg cag act ttc aca atg gtt cta gaa gaa atc tgg aca agt ctt ttc 48
 Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
 1 5 10 15
 atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca gat gaa gtg 96
 Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
 20 25 30
 gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca acc aac atg 144
 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga gaa aca gtg 192
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg tac acg agc 240
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80

cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa ggt cct gag His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu 85 90 95	288
tgt gat gtc act gat gac atc acg gcc act gtg cca tac aac ctt cgt Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg 100 105 110	336
gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc atc ctg aag Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys 115 120 125	384
cat ccc ttt aat aga aac tca acc atc ctt acc cga cct ggg atg gag His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu 130 135 140	432
atc acc aaa gat ggc ttc cac ctg gtt att gag ctg gag gac ctg ggg Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly 145 150 155 160	480
ccc cag ttt gag ttc ctt gtg gcc tac tgg agg agg gag cct ggt gcc Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala 165 170 175	528
gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca gtg cac cta Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu 180 185 190	576
gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc cag aca ttc Glu Thr Met Glu Pro Gly Ala Tyr Cys Val Lys Ala Gln Thr Phe 195 200 205	624
gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca gaa tgt gtg Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val 210 215 220	672
gag gtg caa gga gag gcc act gtg gct gca cca tct gtc ttc atc ttc Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val Phe Ile Phe 225 230 235 240	720
ccg cca tct gat gag cag ttg aaa tct ggt acc gcc tct gtt gtg tgc Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys 245 250 255	768
ctg ctg aat aac ttc tat ccc aga gag gcc aaa gta cag tgg aag gtg Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val 260 265 270	816
gat aac gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca gag cag Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln 275 280 285	864
gac agc aag gac agc acc tac agc ctc agc agc acc ctg acg ctg agc Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser 290 295 300	912
aaa gca gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc acc cat Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His 305 310 315 320	960
cag ggc ctg agc tcg ccc gtc aca aag agc ttc aac agg gga gag tgt	1008

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 325 330 335

tag

1011

<210> 34
 <211> 336
 <212> PRT
 <213> Homo sapiens

<400> 34
 Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
 1 5 10 15
 Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
 20 25 30
 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80
 His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
 85 90 95
 Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
 100 105 110
 Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
 115 120 125
 His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
 130 135 140
 Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
 145 150 155 160
 Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
 165 170 175
 Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
 180 185 190
 Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
 195 200 205
 Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
 210 215 220
 Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val Phe Ile Phe
 225 230 235 240
 Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
 245 250 255
 Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
 260 265 270
 Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
 275 280 285
 Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
 290 295 300
 Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
 305 310 315 320
 Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 325 330 335

<210> 35
 <211> 307
 <212> PRT
 <213> Homo sapiens

<400> 35
 Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1 5 10 15

34

Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
 20 25 30
 Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
 35 40 45
 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60
 Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
 65 70 75 80
 Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val
 195 200 205
 Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
 210 215 220
 Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
 225 230 235 240
 Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
 245 250 255
 Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
 260 265 270
 Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
 275 280 285
 Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg
 290 295 300
 Gly Glu Cys
 305

<210> 36
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 36
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 1 5 10 15

<210> 37
 <211> 32
 <212> DNA
 <213> Homo sapiens

<400> 37
 cgctcgagcc ttccgcaaac ctatgagatc ca

32

<210> 38
 <211> 33
 <212> DNA
 <213> Homo sapiens

<400> 38

35

gcgaattcga gtctaccaaa tgcagacttt cac

33

<210> 39

<211> 18

<212> DNA

<213> Mouse

<400> 39

cgccgcgttc ccgagatg

18

<210> 40

<211> 24

<212> DNA

<213> mouse

<400> 40

ggatgaggca gggctgacaa agtt

24